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RIGHTS AND OBLIGATIONS OF REGULATORS, DRUG MANUFACTURERS, DOCTORS, PHARMACISTS, PATIENTS, AND INSURANCE COMPANIES IN THE CASE OF OFF LABEL USE OF MEDICINAL PRODUCTS

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Abstract

For many years, the off-label use of drugs has been a debated issue for healthcare administrators, regulators, pharmaceutical manufacturers, doctors, pharmacists, insurance companies, and patients. The mechanism for monitoring and regulating the off-label use of drugs must have sound scientific evidence and principles that provide for discouraging their use in the absence of convincing and evidence-based clinical justification and the availability of alternatives. Regulatory authorities (FDA and others) are very strict about manufacturing standards and documentation of the safety and efficacy of drugs, but they do not regulate the way they are prescribed. Thus, doctors can prescribe drugs off-label if their medical knowledge and the patient's condition allow it. The decision to use the drug off-label is not illegal if the doctor does not abuse his official position and does not violate the rules for its prescription.

Keywords: *off label use, pharmacist, doctors, rights and obligations of regulators.*

For many years, the off-label use of drugs has been a debated issue for healthcare administrators, regulators, pharmaceutical manufacturers, doctors, pharmacists, insurance companies, and patients. At present, the requirements and roles of all stakeholders are not clearly defined at the legislative level when prescribing off-label drugs in the world [33, 34]. Thus, the off-label use of drugs should be based on scientific evidence, but the responsibility for the consequences of using off-label drugs lies mainly with doctors. The mechanism for monitoring and regulating the off-label use of drugs must have sound scientific evidence and principles that provide for discouraging their use in the absence of convincing and evidence-based clinical justification and the availability of alternatives. Since the off-label use of drugs has long been common in modern medical and pharmaceutical practice, for many doctors and pharmacists, prescribing drugs off-label is a possible reality. However, the vast majority of patients are unaware that they are taking drugs off label, believing that all of their drugs have been rigorously tested and approved by the regulatory authority [36].

The problem of insufficient knowledge about the off label use of drugs in children has been widely reported regarding the fact that many drugs used in pediatrics do not receive regulatory approval. It is a well-known practice that once a doctor finds a new off-label use useful for more than two patients, he continues to treat other patients without trying to find evidence of such drug use. On the other hand, the American Academy of Pediatrics argues that it is necessary to promote knowledge about off-label use of medications, taking into account the interests of other patients [35, 37].

In the United States, the FDA is authorized by law to review drugs for their safety and effectiveness. FDA approval for the use of drugs has been required since 1938. Manufacturers were required to provide a complete list of ingredients on the label and in the instructions for safe use of medicines due to safety concerns that were identified much earlier when it was revealed that Mrs. Winslow's soothing syrup for teething and colic in children contained morphine and its widespread use has resulted in the death of many babies. In 1962, FDA regulations were strengthened with the additional requirement that new drugs be considered not only for safety but also for their effectiveness. One of the main reasons for the additional regulatory requirements was the 1957-1961 thalidomide tragedy. It wasn't until 1976 that the FDA was given the authority to regulate health care services. Today, the FDA requires drug manufacturers to electronically submit information on the off-label side effects of their drugs, which is readily available to physicians [1].

Consequently, over time, the general scheme for regulating the use of medicinal products in developed countries has become more stringent. To obtain a marketing authorization, manufacturers currently have to provide information on clinical trial results, AR, manufacturing and quality control processes, and how the drug will be marketed. The drugs are then divided into those that can be dispensed over-the-counter and those that require a prescription. The first group consists of medicines requiring parenteral administration, which are inherent in the greatest degree of danger. Prescription-only medicinal products cannot be widely advertised [2].

Each medicinal product, especially a prescription drug, is accompanied by information about it. In some countries, these are instructions for medical use (IFU), in others - a summary of product characteristics (SmPC), in others - an insert leaflet. All this is the result of joint work of regulatory authorities and manufacturers and includes a summary of the safety and efficacy of drugs for specific approved clinical conditions: dosage, duration of administration, warnings and precautions, consequences of drug interactions, data from pediatric or geriatric use experience, as well as specific warnings and contraindications.

Requirements for the instructions have increased enormously over the years. By 2006, the average number of potential ARs indicated in the IFU or SmPC of drugs reached 70 per one medicinal product. Since 2006, there has been a tendency for the information contained in the IFU to increase by about 5-7% per year due to information obtained as a result of post-marketing surveillance and other regulatory prescriptions provided by manufacturers. At the same time, the regulatory authorities did not control medical practice except for the circulation of medicinal products.

When the US Drug Regulatory Act was passed, the FDA and the US Congress expressed concern that the FDA would not regulate medical practice and included a clause on the issue in the 1938 bill. However, in Europe, the EMA still does not control the practice of a medical worker (the existing restrictions for medical workers are determined by professional associations). Thus, even though the regulatory authorities are very strict about manufacturing standards and documentation of the quality, efficacy, and safety of drugs, they do not regulate the process of their prescription and use, since the FDA does not have any authority to enforce responsibility and oversee doctors' work. Therefore, regulators are increasingly aware of the problem associated with the off-label use of drugs, but they cannot interfere with the relationship between doctor and patient. When the FDA proposed legislation to regulate the off-label use of prescription drugs in 1972, the American Academy of Medicine strongly criticized the attempt and it was rejected.

Despite the legal powerlessness of the US regulator to control medical practice, this same obstacle does not work in the opposite direction. The second question related to the legal position is less favorable for the doctor: on the one hand, off label treatment can be a "subject of medical judgment", and on the other, from the point of view of professional responsibility, it can be a manifestation of "medical negligence" associated with off label treatment. Consequently, doctors consider government restrictions on medical practice absolutely unacceptable, they should take full responsibility for the decisions made, i.e. the physician is not legally burdened with the off-label use of drugs, but is bound by professional ethical rules that infringe on his freedom to practice.

Formally, the doctor prescribes what the regulator has not described as safe and effective. Whether such off-label prescribing meets an acceptable standard of care will depend on the level of evidence available to support its use, i.e. on whether the doctor used the evidence as directed. In the United States, the manufacturer must warn the doctor, not the patient, about the risks associated with the off-label use of drugs, since it is the doctor who is responsible for the consequences of the pharmacotherapy. The manufacturer is generally responsible for the quality of the medicine. Typically, if a pharmaceutical product is defective, a patient can file a liability claim against the marketing authorization holder or manufacturer, but in cases where the drug is used off-label, the physician, not the manufacturer, is responsible for any subsequent harm.

In 2011, European pharmacovigilance legislation strengthened the requirement that the manufacturer must inform the authorities about any drug use that does not comply with the on-label [3].

In Germany, as in many other countries, the responsibility for off-label use of drugs is usually with the doctor. The physician is also obliged to inform patients about the off-label therapy and to monitor it. If a patient has suffered from off-label treatment, the doctor is liable under civil and criminal law; however in most civil cases this is covered by personal liability insurance. Finally, along with claims for liability for the quality of drugs, patients can also bring claims for medical malpractice - liability for negligence. Therefore, physicians should be well informed about the medicinal product, justify its use with compelling scientific and reliable medical evidence, and keep records of its use. The medical opinion of the physician must be able to withstand a logical analysis, which in this case implies that physicians should consider the risks and benefits of different treatment options, taking into account the available evidence and the nature of the clinical situation.

Responsibility issues have been particularly raised in the field of oncology, where there is a high medical need for the off-label use of drugs. The Medical Innovation Bill, sponsored by Charles Saatchi, was intended to empower physicians to experiment to improve outcomes for cancer patients. As Saatchi argued, "physicians deciding how to treat a particular patient first recognize that once they deviate from existing standards of care within their profession, they face an automatic and serious risk of being found guilty of negligence if treatment turns out to be less successful than they hoped." His 2013 bill aimed to legally distinguish between reckless experimentation and responsible scientific innovation. However, Saatchi's bill failed to garner government support and succeed in the House of Lords, but it showed that off-label use of

drugs was related to the patient's medical needs and that in severe illness, patients were prepared for greater medical freedom if it accelerated access to treatment [4].

Beyond ethical and legal responsibility, off-label prescribers face the challenge of "reimbursement". Sometimes drug manufacturers refuse to take on this responsibility and place it entirely on the doctor and patient.

The EU document "Measures to regulate the prescription of drugs" contains both restrictions and rules for the prescription of drugs off label, namely:

1) The doctor freely prescribes the off-label drug that he considers necessary to the patient.

2) The physician is not required to obtain informed consent from the patient but is liable for medical malpractice if his actions differ from the standards of treatment.

3) The physician is obliged to evaluate the evidence supporting the therapeutic benefit, safety, financial costs, and possible risks when using drugs off-label.

4) The physician should keep a record of the off-label use of drugs to accumulate information and experience that could form the basis for future clinical trials and ultimately lead to an expansion of indications for an already approved drug.

5) Information for the off-label use of drugs should be based on the most recent clinical evidence, especially if other treatments are not available or are not beneficial to the patient. It must be evidence-based, strictly confined to medical practice, and cannot be used commercially.

6) Sufficient evidence of a balance between the safety and efficacy of the drug must be presented to enable the physician and patient to make informed decisions when considering an off-label prescription.

7) To determine the usefulness of the off-label use of drugs and manage its causes and consequences, the doctor must accurately take into account the purpose of such prescription, the main diagnosis, symptoms, gender, age of the patient, etc.

8) The physician must understand that his patients may have anonymous data to evaluate the safety and effectiveness of this type of treatment. They will articulate these data when a physician uses drugs off-label with minimal benefit and high risk, or as a safe, effective, and alternative drug [5].

The motivation of doctors when prescribing drugs off-label can be different, but, unlike pharmaceutical companies, it is not based on the profit from their sale. Most often it is a desire to test the encouraging information received at conferences and from medical journals in helping patients. The medical profession is an ethical commitment to professional work, not just a "do no harm" principle. As long as the doctor is convinced that it will be safe and effective, he can prescribe the drug off-label, although most patients are unaware that they are taking a drug that may not be approved for a specific use.

In many European countries, there are no legal acts today that would strictly limit the off-label prescription of drugs by doctors. State legislatures can differentiate requirements for informed consent of the patient, the state can also impose regional restrictions on the practice of prescribing drugs off label. Consequently, these requirements can be established and regulated by the state, in particular by its health authorities, and differentiated within the framework of laws on licensing of health services. In some countries, doctors are allowed to prescribe drugs off-label as part of patient care following the Code of Medical Ethics. At the same time, it is important that the doctor has a license to carry out medical activities, does not abuse his powers, summarizes and analyses the results of prescribing drugs off label, and understands that such prescription is, first of all, his sphere of responsibility, but still, he prescribes what the regulatory body would not call safe and effective.

In case of severe illness, patients are ready to exercise more freedom on the part of the doctor, even if this is due to the off-label use of drugs.

Considering the above, it would be optimal to have legal regulation of off-label prescription, but in most countries of the world, the issue of such prescription and use is just beginning to be discussed.

Summing up the reflections on the doctor's responsibility when using off label drugs, the following should be clearly understood: the doctor must be aware of the fact that prescribing drugs off label, he may face serious consequences, especially when there is no convincing evidence of the

effectiveness and/or safety of such drug use. Once this is recognized, the clinician may, reflecting his prescribing practice, ask himself, "Do I prioritize the values of evidence-based medicine or do I prefer other factors such as common professional practice, clinical practice?" The clinician also needs to consider how the patient is informed if at all about off-label use of the drug, as this is a complex ethical and legal issue, given that some off-label prescriptions are supported by substantial evidence, while others are closer to experimental [5].

Pharmaceutical companies typically collect and accumulate information on the off-label use of their drugs, analyze it to determine if it can be published and submitted to regulatory authorities for peer review, and move the drug use from off-label to on-label. With a responsible attitude of the manufacturer to the problem of off-label use of a drug, clinical experience, sufficient in volume and quality, can gradually accumulate, allowing the revision of the instructions for medical use of such drug and make it a drug used on-label. However, a 2001 US study found that 73% of off-label drugs did not have a compelling scientific basis to be prescribed for unapproved indications [6]. Therefore, the FDA encourages manufacturers to publish off-label drug use data in peer-reviewed journals with independent editorial boards requiring the full disclosure of any conflict of interest. Publishing articles about the off-label use of drugs in special supplements or publications sponsored by the manufacturer of these drugs is not recommended.

Sometimes pharmaceutical companies are interested in promoting off-label drug use. Therefore, they involve renowned clinicians in writing articles on the effective and safe use of their drugs off-label and then publishing them in reputable journals to promote such use. This approach is hidden advertising of the off-label use of drugs; however, it allows companies to expand markets, providing additional profit from such use of drugs without prior clinical trials. To a certain extent, this is because the cost of a drug that is used off-label does not differ from the cost when it is used on-label. In addition, research on this issue shows that some pharmaceutical companies are reluctant to publish adverse results on the use of their drugs off label and even threaten those who intend to make this information publicly available.

As for advertising the use of approved drugs or off-label, it should be noted that their advertising has a strict legislative framework, including in Ukraine.

Thus, the Law of Ukraine "On Advertising" defines that "advertising is information about a particular person or a product, distributed in any form or in any way, and intended to form or support the awareness of consumers and their interest in such person or product" [7].

Advertising shall include:

- objective information about the medicinal product, medical device, method of prevention, diagnosis, treatment, rehabilitation and carried out so that it is clear that the message is advertising, and the advertised product is a medicinal product, medical device, method of prevention, diagnosis, treatment, rehabilitation;
- a requirement to consult a doctor before using the medicinal product or medical device;
- a recommendation for mandatory reading of the instructions for use of the medicinal product;
- the following text of the warning: "Self-medication can be
- harmful to your health ", which occupies at least 15 percent of the area (duration) of all advertising" [7].

In addition to the general advertising requirements stipulated by legislation for advertising goods and products, special conditions and additional restrictions are provided for the advertising of medicinal products and medical devices.

What drugs and medical products are allowed for advertising in Ukraine?

The current legislation of Ukraine (Section III "Features of advertising some types of goods", Art. 21 "Advertising of medicinal products, medical equipment, methods of prevention, diagnosis, treatment and rehabilitation "of the Law of Ukraine" On Advertising", S. IV Art. 26 "Information support ”of the Law of Ukraine“ On Medicines") allows advertising:

- "medicines, medical devices, and methods of prevention, diagnosis, treatment, and rehabilitation, which are duly permitted by the

central executive body implementing the state policy in the field of health care, for use in Ukraine";

- "over-the-counter medicinal products that are not included in the list of medicines prohibited for advertising by the central executive body in the field of health care" [7].

In turn, the legislation prohibits advertising of

- "medicinal products, the use and dispensing of which is allowed only with a doctor's prescription, as well as ones included in the list of drugs prohibited for advertising";
- "doping substances and/or methods for their use in sports".

Thus, advertising of registered drugs is partially regulated, but compliance with legislation in this matter over is not controlled everywhere. Thus, the current legislation prohibits advertising of prescription drugs, as well as over-the-counter drugs, included in Order No. 876 of the Ministry of Health of Ukraine "On Approval of the List of Over-The-Counter Medicinal Products Forbidden for advertising" dated 06.11.2012 [8].

The decision to refer a specific drug to the list of medicinal products, prohibited for advertising is made by the Ministry of Health of Ukraine during state registration (re-registration) of medicinal products based on recommendations of the State Expert Center of the Ministry of Health under the criteria that are used to determine medicinal products whose advertising is prohibited (Order No. 422 of the Ministry of Health of Ukraine dated 06.06.2012) if at least one of the following conditions is met:

- "dispensing of the medicinal product is carried out only on prescription";
- "the medicinal product contains narcotic products, psychotropic substances, and precursors";
- "the use of the medicinal product may cause a habituation syndrome, as specified in the instructions for medical use, except for drugs for external (local) use";
- "The medicinal product is used exclusively for the treatment of women during pregnancy and breastfeeding";
- "the medicinal product is used exclusively for the treatment of children under 12 years";
- "the medicinal product is used to treat tuberculosis; sexually transmitted diseases; especially dangerous infectious diseases; HIV / AIDS; cancer and other tumors; chronic insomnia; diabetes; obesity (including drugs used to lose weight); impotence (erectile dysfunction)".

Information that a drug is prohibited for advertising is entered into the State Register of Medicines of Ukraine.

Advertising of medicinal products and medical devices must correspond to the officially approved information about this medicinal product and cannot contain information about therapeutic effects for the treatment of diseases that can not be treated or are difficult to treat.

Advertising must adhere strictly to approved indications and conditions of use to comply with officially approved drug information. For example, if a drug has been approved for epilepsy only, the manufacturer cannot advertise it for bipolar disorder or depression.

At the same time, in the advertising of medicinal products it is prohibited to provide:

- information that may give the impression that at the use of the medicinal product or medical device, consultation with a specialist is not necessary;
- information that the therapeutic effect of the use of the medicinal product or medical device is guaranteed;
- images of changes in the human body or its parts as a result of illness, injury;
- statements that contribute to the emergence or development of fear of getting sick or worsening health due to the non-use of drugs, medical devices, and medical services that are advertised;
- statements that contribute to the possibility of self-diagnosis for diseases, pathological conditions of a person and their self-treatment using medical products that are advertised;
- references to medicinal products, medical devices as the most effective, the safest, exclusive in terms of the absence of adverse reactions;
- comparisons with other medicinal products, medical devices to enhance the advertising effect;
- references to specific cases of successful use of drugs, medical devices;
- recommendations or links to recommendations of medical professionals,

scientists, medical institutions, and organizations regarding the advertised product or service;

- acknowledgments, letters, excerpts from them with recommendations,
- stories about the application and results of the action of the advertised product or service from individuals;
- images and mentions of the names of celebrities, heroes of films, television and animation films, authoritative organizations;
- information that may mislead the consumer regarding the composition, origin, effectiveness, patent protection of the goods being advertised.

Also, the participation of doctors, other healthcare professionals, and persons whose appearance imitates the appearance of doctors is prohibited in the advertising of medicinal products and medical devices [7].

Moreover, Part 13 of Art. 21 "Particularities of advertising of certain types of goods" of the Law of Ukraine "On Advertising" stipulates that the above provisions do not apply to advertising of medicinal products, medical devices, methods of prevention, diagnosis, treatment, and rehabilitation, which is distributed (presented) in specialized publications intended for medical institutions and doctors, announced at seminars, conferences, symposia on medical topics [7].

The Law of Ukraine "On Advertising" also stipulates what information is strictly prohibited to be included in advertisements for medicinal products and medical devices. For example, "Advertising of new methods of prevention, diagnosis, rehabilitation and medicines that are under consideration in the prescribed manner, but not yet approved for use is prohibited" (Part 11, Art. 21 "Particulars of advertising of certain types of goods"). This norm contradicts the innovations that were fixed in the framework of expanding the therapeutic possibilities of using drugs in the treatment of coronavirus disease in March 2020 by the relevant law of Ukraine [9, 10,]. That is, in Ukraine, there is no possibility of advertising the off-label use of drugs. Whereas in the United States, advertising and non-advertising promotions of the off-label use of drugs have been regulated, and this requires a «fair balance» of information in advertising about the benefits and risks of drugs. This means that information about the adverse effects of the drug should be included in every type of advertisement. In countries without this provision of legislation, the text of the advertisement does not always contain information about the risks associated with the use of the medicine. In addition, to advertise any drug, the manufacturer must obtain approval from the FDA or from the municipality where the drug is manufactured.

In China, off-label advertising is strictly prohibited, but control over this process remains weak. Advertisers cannot be held criminally liable for advertising violations, and administrative and civil penalties are often too small to be a deterrent. Although physicians can decide to prescribe a drug off-label for a specific purpose, drug regulators do not allow pharmaceutical companies the freedom to decide whether to advertise it off-label for a specific purpose [12].

Likewise, advertising for off-label use of drugs is banned in many other countries, but the fines imposed for violations are too low to be a sufficient deterrent, so consumer and consumer rights protection legislation may act as the primary protection for patients. In addition, governments in many countries are largely opposed to promoting unapproved drugs rather than advertising.

Regulatory authorities (FDA and others) are very strict about manufacturing standards and documentation of the safety and efficacy of drugs, but they do not regulate the way they are prescribed [14].

In 2009, the FDA issued a new document that tightened previous rules: pharmaceutical companies can disseminate information about the use of drugs off label to medical professionals, managers of the pharmacy network, persons responsible for health insurance of patients, provided that they actively seek regulatory approval for such use of medications soon. However, it is easier to obtain off-label use approval in the United States than in Europe, so about 30% of drug prescriptions in the United States are off-label [12].

In 2017, in the United States, the Arizona state legislature passed the Free Speech Medicine Act. The law prohibits the punishment of a pharmaceutical manufacturer, its representatives, or pharmaceutical workers for "truthfully promoting" the off-label use of drugs, and also makes it possible to freely communicate any useful

off-label drug alternatives. Opponents of the law feared that drug manufacturers would use drugs off-label as an easier route to widespread distribution without the strict controls of the traditional multi-step FDA approval process. In any case, Arizona law attracted the attention of many other state legislatures in the United States, which ultimately passed their own versions of the Free Speech Medicine Act. Federal courts have also responded favorably to this initiative: "The government cannot prosecute pharmaceutical manufacturers for an off-label using of FDA-approved drug for which doctors have found new and useful uses" [15].

However, to avoid potential harm from inappropriate off-label prescriptions, the FDA punishes manufacturers for directly promoting the unlicensed off-label use of their drugs. Such companies are subject to fines for illicit marketing of off-label drugs, and the magnitude of such fines, as a rule, exceeds the profit from the off-label application. For example, in 2012, the pharmaceutical company GlaxoSmithKline was forced to pay a $ 3 billion fine for the resolution of healthcare fraud. The charges concerned the antidepressant Paxil for children and adolescents, which was not approved for use in children because it was ineffective and potentially dangerous in this patient population [16].

The problems described above lead to serious litigation between pharmaceutical manufacturers and their competitors, consumers, or fair trade organizations for misuse of drugs. During 2003-2008 more than a dozen cases were initiated against manufacturers of drugs that were used in violation of their on-label prescription, and as a result, these firms paid significant fines to the plaintiffs [49].

Thus, in 2010 Johnson & Johnson pleaded guilty to promoting Topamax (topiramate) on the market for unauthorized indications and paid a fine of $ 81.5 billion, of which $ 6.1 million - a criminal fine. Topiramate, approved for the treatment of epilepsy, has been prescribed off-label without clinical trials for the treatment of bipolar disorder and alcohol dependence. The company's actions were qualified by the court as illegal. The world's largest pharmaceutical company, Eli Lilly, paid out about $ 1.48 billion for the use of the atypical antipsychotic Zyprexa (olanzapine) for the treatment of dementia in the elderly or Alzheimer's disease without specifying these indications for medical use.

Another example is Pfizer's anti-inflammatory drug Bextra (the non-steroidal anti-inflammatory drug valdecoxib), which has been approved for the treatment of arthritis and menstrual pain but has been advertised as an off-label drug for the treatment of acute pain of any origin. In September 2009, Pfizer paid out $ 1.3 billion for advertising the off-label use of Bextra and three other medicines.

An example of a lawsuit filed under the False Claims Act is a lawsuit that resulted in AstraZeneca paying a $ 520 million fine to resolve all civil and criminal disputes regarding the illegal promotion of the antipsychotic drug seroquel. Pfizer paid a $ 430 million fine in 2004 due to the drug gabapentin (Neurontin). It was approved as an anticonvulsant drug, but the company advertised its use off-label for pain relief, attention deficit hyperactivity disorder (ADHD), migraine, and other conditions that were not listed in the drug's instructions.

Bristol-Myers Squibb paid a $ 515 million fine in 2007 for advertising the drug Abilify (aripiprazole), which was approved for the treatment of schizophrenia and bipolar disorder in adults, but the company also promoted the drug for use in children with psychoses caused by dementia.

Over the past decade, 17 pharmaceutical companies have paid more than $ 16 billion for off-label drug promotion violations.

On the one hand, control over the prescription of off-label drugs in most cases is an unregulated process, and the fines for violations of their prescription are incommensurable in comparison with the profit generated from the sale of such use. According to some experts, pharmaceutical companies view such fines as mere costs of doing off-label business. However, manufacturers stop promoting the off-label use of drugs and even discourage their prescription if it increases their costs.

On the other hand, some off-label drug manufacturers may not have the financial resources to conduct formal clinical trials for unapproved indications. In this situation, the FDA authorizes changes in the indications and warns doctors to be careful when prescribing these drugs and that this practice includes both benefits and risks. Since 1997,

the FDA has relaxed its off-label rules, which stipulate that a manufacturer must:

- provide the FDA with proposals for a new indication for the use of drugs off label;
- indicate where clinical studies have been published for a new indication for the use of drugs off label: in a journal, in another peer-reviewed publication, or a medical reference book;
- provide the manufacturer's documentation or permission to approve a new indication or features of the use of drugs off label;
- be aware that the clinical use of drugs off-label can lead to serious civil and criminal penalties [14, 17, 18, 19].

No less serious is the financial side of the issue of using off-label drugs, when it comes to the possibilities of the patient and the conditions of insurance companies, especially in the case of using expensive drugs. Insurance companies are well aware that more aggressive promotion of off-label drug use can have significant financial implications to cover the cost of such treatment. Therefore, health insurance companies carefully check and analyze the off-label use of drugs. In most cases, insurance companies are reluctant to reimburse the cost of treatment outside the approved indications or fully reimburse the cost of treatment, especially in the past ten years. Insurance companies are increasingly questioning the need to pay for drugs that have not been proven effective and safe in formal clinical trials.

In 1993, the United States passed a federal law that obliged insurance companies to cover the cost of using drugs off-label for cancer. The law obliges to cover the costs of using drugs off label, if there is a scientific basis, or if the drugs have been subjected to clinical trials [20].

In 2008, Medicare rules were changed, allowing for increased off-label use of drugs, especially for the treatment of cancer. However, off-label health insurance regulations are still strict and difficult to enforce. If a physician intends to prescribe a drug off label, he or she should carefully review the patient's coverage program

and provide insurance companies with copies of peer-reviewed journal articles or other authoritative sources that provide evidence to support its off-label use.

Another problem is that off-label prescribing is usually not in line with the "standard of care". It is an area of legal risk, especially in the case of an unfavorable outcome of a patient's treatment with a drug used off-label [21, 22].

For example, in Germany, the Federal Social Committee decided back in 2002 that off-label therapy should be funded if: the disease is severe, there is no other treatment, and there is sufficient scientific evidence that the drug used is necessary for successful treatment [23, 24].

France has a complex system that offers different reimbursement terms depending on where the medicine is prescribed. Outside the hospital, off-label drug use is not covered, while hospital use does cover the cost of inexpensive off-label drugs [25].

In Canada and the UK, insurance companies reimburse off-label drug use, but in Japan, they do not [26, 27].

In the United States, off-label prescriptions are usually not covered by health plans because they are considered experimental. In 1993, the Consolidated Budget Reconciliation Act allowed the off-label use of anti-cancer drugs if there was evidence of their effectiveness in high-level evidence compilations [31].

As for the severity of the disease, there are different approaches to its definition. For example, the FDA considers a disease to be severe if it meets such criteria:

- the disease poses a potential threat to the patient's life;
- no other/alternative treatment is available;
- the disease causes irreparable damage to health or may cause permanent disability of the patient;
- the disease necessitates a long hospital stay;
- the disease can cause congenital anomalies and defects that pose a constant threat to health;
- the disease causes difficulties and disruptions in daily life [1].

In most cases, the absence of other treatment is the criterion that is easy for the insurance company to check, since national and international standards, clinical guidelines, and patient treatment protocols are publicly available. In early 2012, a law came into force in the United States that states: "An insured patient with a life-threatening or fatal illness for

whom there is no generally accepted medical standard may appeal for reimbursement of treatment if there is a chance of recovery or a positive effect from the proposed treatment." [32].

As for the presence of sufficient convincing evidence that the off-label use of a drug is necessary for successful treatment, this criterion should be established after evaluating its clinical efficacy and safety, as well as economic availability compared with the available pharmaceutical alternative. If it turns out that the alternative is inferior in these criteria to the use of the drug off-label, a decision can be made in its favor. Analysis of court decisions shows that insurance companies reimburse off-label use of drugs in most but not all cases.

The use of drugs off-label is a cause of concern for patients, as they often do not know that drugs are not prescribed to them according to the instructions and there is a risk that they are not indicated for them, moreover, they can be dangerous to health. This risk especially increases if the pharmaceutical company, knowing about the potential risks from the off-label use of drugs, does not inform doctors and pharmacists about it. In the latter case, patients are aware of the important benefits of using the drug off-label but are unaware of the dangers of harm from it. Patients can also suffer from doctors' failure to disclose facts about the licensed status of a drug, lack of evidence regarding the safety and efficacy of drugs, thus violating their rights [30]

Patients have the right to independently decide (in case of informed consent) whether they will take the drug off label. Patients cannot be the subject of medical experiments without their consent and experience the possible risks of prescribing drugs off-label.

The drugs should be used off-label only under the supervision of a physician and pharmacist to avoid the adverse effects of self-medication. The pharmacist in the pharmacy must inform the patient about the peculiarities of using the drug if he becomes aware that the drug is planned to be used off-label, and must provide adequate information about the adverse effects in this case. As a result of timely information provided by the pharmacist, some ARs can be avoided [28, 29]

Thus, doctors can prescribe drugs off-label if their medical knowledge and the patient's condition allow it. The decision to use the drug off-label is not illegal if the doctor does not abuse his official position and does not violate the rules for its prescription.

References

1. Tabarrok A. T. Assessing the FDA via the anomaly of off label drug // Independant Review. – 2000. – Vol. 5 (Iss. 1). – P. 25–53.
2. Delpeuch A., Leveque D., Rob L.et al. Off-label use of oxaliplatin in patients with metastatic breast cancer // Anticancer Res. – 2011. – Vol. 31 (Iss. 5). – P. 1765–1767.
3. Eguale T., Buckeridge D. L., Winslade N. E. et al. Drug, patient, and physician characteristics associated with off label prescribing in primary care // Arch. Intern. Med. – 2012. – Vol. 172, N 10. – P. 781–788.
4. Cavalla D. Off-label Prescribing: Justifying Unapproved Medicine. Hoboken, NJ, Wiley-Blackwell, 2015, 216 p.
5. Hill P. Off licence and off label prescribing in children: Litigation fears for physicians // Arch. Dis. Child. – 2005. – Vol. 90. – P. 17–18.
6. Lai L. L., Koh L., Ho J. A. et al. Off-label prescribing for children with migraines in U.S. ambulatory care settings // J. Manag. Care Spec. Pharm. – 2017. – Vol. 23, N 3. – P. 382–387.
7. Law of Ukraine "On Advertising", approved by a resolution of the Supreme Council of Ukraine of July 3, 1996 № 271/96-VR. – https://zakon.rada.gov.ua/laws/show/270/96-%D0%B2%D1%80#Text
8. Order of the Ministry of Health of Ukraine "On some issues of banning the advertising of medicines" from 06.06.2012 № 422. – https://www.apteka.ua/article/153176
9. Order of the Ministry of Health of Ukraine "On approval of the list of drugs prohibited for advertising, which are available without a prescription "from 06.11.2012 – https://zakon.rada.gov.ua/laws/show/z1948-12#n13
10. Law of Ukraine "On Amendments to certain laws of Ukraine concerning the treatment of

coronavirus diseases (COVID-19) as amended by the Law of Ukraine of March 30, 2020 № 539-IX.

11. Law of Ukraine "On Amendments to certain laws of Ukraine on ensuring the treatment of coronavirus disease (COVID-19) as amended and amendments introduced by the Law of Ukraine of June 19, 2020 № 737-IX. – https://zakon.rada.gov.ua/laws/show/737-20#n2
12. Order of the Ministry of Health of Ukraine № 762 "On approval of the protocol" provision of medical care for the treatment of coronavirus disease (COVID-19)" from 02.04.2020 – https://moz.gov.ua/article/ministry-mandates/nakaz-moz-ukrainivid-2042020–762-pro-zatverdzhennja-protokolu-nadannja-medichnoi-dopomogidlja-likuvannja-koronavirusnoi-hvorobi-covid-19
13. Zen L. De, Marchetti F., Barbi E. et al. Off-label Drugs Use in Pediatric Palliative Care // Italian J. of Pediatrics. – 2018. – Vol. 44 (Iss. 1). – P. 1–6.
14. Stafford R. S. Regulating off label drug use: rethinking the role of the FDA // N. Engl. J. Med. – 2008. – Vol. 358 (Iss. 14). – P. 1427–1429
15. Orentlicher D. Off label drug marketing, the first amendment and federalism // Wash. Univ. J. Law. Policy. – 2016. – https://openscholarship.wustl.edu/law_journal_law_policy/vol50/iss1/4/
16. Skånland S Sigrid, Cieślar-Pobuda Artur. Off-label Uses of Drugs for Depression // Eur. J. of Pharmacology. – 2019.2019 Dec 15;865:172732. doi: 10.1016/j.ejphar.2019.172732
17. Tabbarock A. From off label prescribing towards a new FDA // Med. Hypotheses. – 2009. – Vol. 72. – P. 11–13.
18. Repucci N. An examination of off label marketing and promotion: settlements, issues, and trends // J. of Health Care Compliance. – 2011. – Vol.13. – P. 15–21.
19. Rogers J. Freedom of speech and the FDA's regulation of off label drug uses // The George Washington Law Review. – 2008. – Vol. 76 (Iss. 5). – P. 1429–1443.
20. Thomas K. Ruling is victory for drug companies in promoting medicine for other uses. The New York Times, 2012. – Available at: https://www.nytimes.om/2012/12/04/business/ruling-backs-drug-industry-on-off-label-marketing.html
21. Levinson D. Medicare atypical antipsychotic drug claims for elderly nursing home residents. Department of Health and Human Services Office of Inspector General Report (OEI- 07-08-00150). (2001). – https://oig.hhs.gov/oei/reports/ oei-07-08-00150.pdf
22. O'Connell E., Rosebush L. H.FDA Published Guidance on Off-Label Use Communications. – 2017.
23. Popovici I., Lai L., Lopez-Evangelio F. Non-Medical Use of Prescription Drugs and Health Services Utilization // J. Develop. Drugs. – 2013. – Vol. 2. – P. 104–108.
24. Schröder C., Dörks M., Kollhorst B. et al. Outpatient antidepressant drug use in children and adolescents in Germany between 2004 and 2011 // Pharmacoepidemiol. Drug. Saf. – 2017. – Vol. 26, N 2. – P. 170–179
25. Drogou François, Netboute A., Giai J. et al. Off-label Drug Prescriptions in French General Practice: A Cross-Sectional Study // BMJ Open. – 2019. – Vol. 9 (Iss. 4). – P. 1–8.
26. Brown Gregory P., Stewart L. A., Rabinowitz T. et al. Approved and off-label use of prescribed psychotropic medications among Federal Canadian Inmates // The Canadian J. of Psychiatry. – 2018. – Vol. 63 (Iss. 10). – P. 683–691.
27. Chisholm A. Exploring UK attitudes towards unlicensed medicines use: A questionnaire-based study of members of the general public and physicians // Int. J. Gen. Med. – 2012. – N 5. – P. 27–40.
28. Edwards I. R. Off label pharmacovigilance // Drug. Safety. – 2011. – Vol. 34, N 10. – P. 795–797.
29. Wittich C. M., Burkle C. M., Lanier W. L. Ten common questions (and their answers) about Off-label drug use // Mayo Clin. Proc. – 2012. – Vol. 87, N 10. – P. 982–990.

30. Rich B. A. Off-label prescribing: In search of a reasonable patient-centered approach // J. Pain Palliat. Care. Pharmacother. – 2012. – Vol. 26, N 2. – P. 131–133.

31. Walton S. M., Schumock G. T. et al. Developing evidence-based research priorities for off label drugs Parliament and of the Council on orphan medicinal products, Agency for Healthcare Research and Quality (AHRQ) (Developing Evidence-Based Research Priorities for Off-label Drug Use) // Effective Healthcare Research Reports. – 2009. – Vol. 1. – P. 33–38.

32. Stafford R. S. Regulating off label drug use: rethinking the role of the FDA // N. Engl. J. Med. – 2008. – Vol. 358 (Iss. 14). – P. 1427–1429.

33. Causes and legal aspects of the off label drugs emergence: literature review / Kalko K. O., Drogovoz S. M., Komarova A. P., Hailat I. A., Drogovoz K. V., Ivantsyk L. B. Pharmacologyonline. Vol. 3. 2021. P. 179-186. https://pharmacologyonline.silae.it/files/archives/2021/vol1/PhOL_2021_1_A024_Kalko.pdf.

34. Modern medical and pharmaceutical problems of off label drug use: literature review / Drogovoz S. M, Komarova A. P, Kalko K. O, Panfilova A. L., Orlenko I. V., Khalieieva O. L., Belik G. V. Pharmacologyonline. 2021. Vol. 2. P. 55-61. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A007_Drogovoz.pdf.

35. Frequency of off-label drug use in medicine / Drogovoz S. M., Shchokina K. G., Komarova A. P., Kalko K. O., Orlenko I. V., Belik G. V., Fesenko W. Yu. Pharmacologyonline. 2021. Vol. 2. P. 138-144. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A017_Drogovoz.pdf.

36. Positive and negative aspects of the off-label drugs use / Drogovoz S., Kalko K., Tsyvunin V., Horoshko V., Levkov A., Verholias O., Zhurenko D. Pharmacologyonline. 2021. Vol. 2. P. 1179-1185. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A132_Drogovoz.pdf

37. Kalko K. O. «Korvitin®» - new therapeutic opportunities Pharmacologyonline. 2021. Vol. 2. P. 1310-1316. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A144_Kalko.pdf.