PharmacologyOnLine
Archives • 2021 • vol.3 • 1723-1736

# THE OFF-LABEL USE OF DRUGS IN PEDIATRICS

*Kalko Kateryna[1], Drogovoz Svitlana[1], Khodak Larysa[2], Mogilievska Svitlana[3], Vynogradova Galyna[4], Artiukh Tetiana[1], Svyshch Olena[5]

[1]National University of Pharmacy, Kharkiv, Ukraine
[2]Kharkiv Medical Academy of Postgraduate Education, Kharkiv, Ukraine
[3]Institute of Pediatrics, Obstetrics and Gynecology named after acad. O. M. Lykyanova of the NAMS of Ukraine, Kyiv, Ukraine
[4]Education and Research Center - Ukrainian Family Medicine Training Center of Bogomolets National Medical University, Kyiv, Ukraine
[5]Izmail State University of Humanities, Izmail, Ukraine
*ketrin27kalko@gmail.com

**Abstract**

In pediatrics, the optimal from the point of view of medical tactics, ethics and interests of a sick child is the use of approved drugs. However, in the absence of drugs approved by the regulatory authorities, the pediatrician is sometimes forced to use drugs off label, based on personal experience or available scientific evidence. The results of the analysis of the range of drugs used to treat children indicate that doctors often prescribe them off label. But this places a great responsibility on them. Prescribing drugs is not an easy task for pediatricians, since their range in pediatrics is about 2/3 less than in adult patients. Therefore, in pediatrics, treatment with drugs off label is the rule rather than the exception. This is due to the fact that the traditional way of promoting drugs in pediatric practice differs from the usual way and includes several stages. Firstly, at the first registration, a medicine is allowed for use only in adult patients, and secondly, permission to conduct its clinical trials in pediatric practice is granted only when its efficacy and safety of use in adult patients is confirmed. Most of the pediatric off label drug use data comes from clinical trials in adult patients, but full extrapolation of this data to children is not correct. A growing organism differs from an adult in the state of the receptor apparatus, the mechanisms of absorption, biotransformation, excretion processes, the qualitative and quantitative composition of the protein fractions of blood plasma, etc. This not only changes the pharmacodynamics and pharmacokinetics of the drug, but also determines the characteristics of the use of drugs in children. Moreover, the drugs can specifically affect the physical and cognitive development of the child, bone tissue, immune and puberty. All these facts require clinical trials of drugs with the participation of children as subjects, however, the frequency of such trials remains low (sometimes for objective reasons). That is why at this time the question of the high frequency of off label drug use in remains very relevant in medicine.

**Keywords**: *pediatrics, off-label use, children.*

In pediatrics, the optimal from the point of view of medical tactics, ethics and interests of a sick child is the use of approved drugs. However, in the absence of drugs approved by the regulatory authorities, the pediatrician is sometimes forced to use drugs off label, based on personal experience or available scientific evidence. The results of the analysis of the range of drugs used to treat children indicate that doctors often prescribe them off label [36, 94, 97, 51, 46]. But this places a great responsibility on them. [1, 65].

Prescribing drugs is not an easy task for pediatricians, since their range in pediatrics is about 2/3 less than in adult patients. Therefore, in pediatrics, treatment with drugs off label is the rule rather than the exception. This is due to the fact that the traditional way of promoting drugs in pediatric practice differs from the usual way and includes several stages. Firstly, at the first registration, a medicine is allowed for use only in adult patients, and secondly, permission to conduct its clinical trials in pediatric practice is granted only when its efficacy and safety of use in adult patients is confirmed [3, 7, 80, 49].

Also, the problem of prescribing drugs off label children due to the fact that the introduction of new indications in the instructions, the expansion of the approved age range of doses of drugs, initiated by pharmaceutical companies, requires appropriate clinical trials in the pediatric population, which are laborious, expensive and, in many cases, economically or ethically unreasonable [13, 71, 37, 78].

Also, drugs for children are still a much less profitable segment of the pharmaceutical market. Therefore, for the majority of manufactured drugs (65–80%), clinical trials on children have not been carried out. However, the need for safe and effective drugs in pediatric practice remains extremely high. [95, 57].

As stated above, one of the most important reasons for prescribing medication off label in children, there is a lack of data on the efficacy and safety of their use and on clinical trials of drugs approved by the regulatory body [62] with a specific disease or condition in children due to the difficulties of their implementation. For example, laboratory procedures in clinical trials that seem technically simple for adults (taking a blood test or obtaining a urine sample) can cause difficulties or discomfort in children. Ethical and legal issues in children are difficult or not always resolved: adults can give informed consent to participate in a clinical trial, but children can not, because "consent" means a full understanding of the potential risks when taking the studied drugs. According to requirements GCP in clinical trials of new drugs, parents decide to participate in a clinical trial of children under 7 years of age [1]. However, about 59.8% of the parents surveyed will allow their children to take part in clinical trials only if the disease is dangerous for the child's life; 40.2% of respondents would agree to a clinical trial only if the child is at risk of developing a chronic or serious illness. In fact, the percentage of parents who would allow their children to take part in clinical trials is much lower. At the same time, only 30% of the parents surveyed know that drugs can be prescribed to children for unregistered indications, although 73% of them believe that unapproved drugs are illegal [96].

Despite measures to increase the number of clinical trials involving children by USA and EU regulators [16, 29, 32], they remain limited. Therefore, if a drug is not registered for use in the pediatric population, doctors prescribe it based on their own point of view, their own opinion and experience in order to make a decision to treat the child with drugs off label, including the dose, method and frequency of its administration, etc. To do this, they monitor and take into account the effectiveness and safety of drugs off label in adult patients, as well as the positive experience of colleagues obtained when prescribing off label drugs in children. They often use a generic drug introduction approach off label, which is based on the use of data obtained from adults, but adjusting the dose depending on the weight or age of the child. However, it should be noted that the indicators of pharmacokinetics and pharmacodynamics of drugs can have significant differences in different age groups, which can significantly affect their effectiveness and cause adverse effects of drug use.

The most common reasons for medication use off label in pediatric practice are:

- ✓ use in an age group of patients for which the drug has not been approved;

- ✓ use of a drug that has no indication for a specific disease, when most drugs from the same pharmacological group have been approved for its treatment;
- ✓ prescribing a drug to save a child's life.

Sometimes doctors in therapy off label do not take into account the pathophysiological features of diseases in children and prescribe the same drug for all such diseases, despite the fact that it is recommended only for one of these diseases. For example, the use of metformin for the treatment of diabetes mellitus in an insulin-resistant patient.

Testing of medicines for children is being carried out FDA – one of the most stringent regulatory authorities in terms of procedures, whose main task is to ensure the highest level of safety and efficacy of drugs [15]. The first law to stimulate the creation of drugs for children was passed FDA more than 20 years ago, it was followed by a series of laws aimed at improving the efficiency and safety of research of new drugs in pediatric practice (2002, 2003 years). Today, only about 20% of drugs are approved FDA, have indications for use in pediatrics in the instructions [15, 34]. Therefore, if necessary, doctors prescribe drugs for children off label, but their use is based only on safety and efficacy data from adequate, well-controlled clinical trials in adults.

In 2012, one of the professional associations of pediatric practitioners in the United States issued a statement regarding the use of drugs off label in children [15]. It notes that the prescription of the medicine off label cannot be wrong if it is based on scientific evidence, experienced medical judgment or published scientific literature [41, 54].

Various national and international studies indicate that the frequency of prescribing off label can range from 18 to 60% in young children and up to 90% in newborns [19, 43]. Many studies have shown that pediatric patients aged 0 to 2 years were more likely to receive off label drugs than in any other age group [5].

For newborns and adolescents today, most drugs used in adult patients are not licensed [8, 14, 89]. So, when analyzing pharmacotherapy in pediatric emergency departments in the United States, it was found that about 70% of drugs are prescribed off label, and the level of such drug use in pediatric intensive care units is higher (58%) than in any other departments. It was also found that antibiotics, analgesics, antiepileptic drugs for the treatment of diseases of the nervous system in children are often prescribed off label [87, 58]. In the United States and Portugal, about 82% of drugs affecting the respiratory system and 31% of inhaled corticosteroids for children are prescribed off label. Various combinations of antihistamines, anti-inflammatory drugs and analgesics are prescribed for small patients in off label doses [88]. Paracetamol, widely used to treat fever and pain in children, is often prescribed off label by dose or age. Although lorazepam and ondansetron are also widely prescribed off label, this is based on the results of clinical trials in pediatrics.

Drugs that affect the respiratory system are often prescribed for children and most of them are officially approved for the treatment of bronchial asthma at a particular age [11, 86]. In young children, the diagnosis of asthma is difficult due to age-related changes in lung function, therefore, the degree of use of off-label drugs in them has been quantitatively assessed in only a few studies. Bronchodilators are most commonly used off label to treat acute bronchitis or upper respiratory tract infections [21, 24, 44, 81]. Off-label prescription of nitric oxide, inhaled salbutamol (42%), oral clenbuterol / ambroxol (20.7%) and caffeine in pediatrics for idiopathic apnea is common [60, 68].

There are many publications around the world on the use of off label drugs in children. So, for example, in the USA [27, 66, 69, 74], Germany [28, 42, 45, 72, 77, 83], Brazil [42, 83], Australia [61, 73] and many other countries [12, 28, 47, 48, 52, 53, 55, 56, 63, 64, 67] there is a high frequency of prescribing off label drugs in children's hospitals - from 72 to 93% [61].

Studies of the use of off label drugs in pediatrics have shown that they are most often used at a dose other than the recommended dose. There are various approaches to calculating the dose for a child: based on the child's body weight and age, depending on the area of his body, and also empirically. Inappropriate dosing of off label medications in pediatrics can carry potential risks to both the patient and the clinician. Thus, the drug can be used in an insufficient or overestimated dose, which, in turn, can lead to the problem of ineffective treatment or overdose. For a doctor, the

use of the drug in an inappropriate dose can also have adverse consequences and even end in legal proceedings.

Studies conducted in Germany in 2004-2013 showed that during the analyzed period 22% of off label drugs prescribed were used at a dose different from the recommended dose, in 4.3% of cases - for unregistered indications, in 3.8% - in children of other age categories, and not those that have been officially approved. The frequency of such prescriptions was higher in boys (41.4%) than in girls (38.9%), especially in the age group from 3 to 6 years (48.7%). It should be noted that 61.2% of off label drug use was associated with self-medication [136, 72].

Many studies of American scientists have studied the use of off label drugs in different age groups and the frequency of such prescription was established depending on age: 76% - in the age group from 1 to 2 years, 69% - in the group from 1 to 12 months [16].

As part of the regulatory policy of pharmacotherapy in children in the United States, a "coercive and reward" mechanism has been created to increase the range of pediatric drugs in the pharmaceutical market. Laws were the source of the compulsory function «Best Pharmaceuticals Children Act – BPCA», adopted in 2002, and «Pediatric Research Equality Act – PREA», adopted in 2003, according to which the conduct of pediatric research is a mandatory requirement for the registration of new drugs in accordance with the established requirements in all age groups. This applies to both off label and approved drugs. In this case, the promotion is realized through the provisions of the BPCA, which provide for an additional 6 months of exclusive rights to use drugs off label in children.

To extend the duration of these exclusive rights, a pharmaceutical manufacturer must provide the FDA with the results of clinical trials using certain dosage forms in different age groups. An important requirement is the provision of information on PR, registered drugs at the stage of post-marketing research.

FDA believes that off label prescribing represents an alternative based on extensive clinical experience and supporting evidence of efficacy and safety, especially when no approved alternatives exist. Particularly high rates of off-label use of pediatric drugs were observed in inpatient settings (36–92%) [4, 15, 82].

The majority of off label prescriptions in the French health care base were for cardiovascular (67.2%) and for the treatment of diseases of the genitourinary system. The use of off label drugs in children under 2 years of age is often associated with the treatment of diseases of the sensory organs, diseases of the respiratory system, and the systemic use of antimicrobial agents. In children from 3 to 10 years old, most off label prescriptions were associated with drugs that are used for diseases of the gastrointestinal tract and metabolism, while in the older age group (from 11 to 17 years old) - with drugs for the treatment of diseases of the gastrointestinal tract, sensory organs and skin [30, 31].

According to the ATC drug classification, off-label antihistamines were the most common, followed by penicillins, macrolides in combination with clindamycin, antidepressants and cephalosporins. Often prescribed off label antidepressants were sertraline (93%) and fluoxetine (37%), as well as the nonsteroidal anti-inflammatory drugs ibuprofen and diclofenac sodium.

Off label appointments have increased over time - 47.2% in 2012–2015. against 41.9% in 2006-2008. These results are also in line with the global trend of decreasing antibiotic prescriptions over the past 20 years, especially penicillins and cephalosporins. [18, 20].

Studies conducted in France have shown that age or dose is a common cause of off label prescription in children, as well as relatively high rates of off label prescription of antihistamines and antibiotics. [18].

One of the main directions of development of the pharmacotherapeutic pediatric sector in the United States is the development of cooperation with the National Institutes of Health. The FDA is working with the National Institutes of Health to formulate a list of drugs for pediatric clinical trials to assess their safety and efficacy in accordance with the provisions of the HRCA law. For the financial support of this activity, appropriate changes were made to Public Health Service Act (PHSA) and a special research fund with a budget of $ 200 million was created. Later, during the revision of the ARCA Law in 2007, the initiative was re-supported.

However, this time, the list of drugs, which is updated every three years, was formed from the priority areas of research activities in the field of therapeutic pediatrics. [25, 26].

Thanks to these laws in 2003-2007. The FDA has made more than 500 changes to pediatric drug guidelines. These changes expand both pediatric information in off label drug labeling and a knowledge base that clinicians can use to inform their therapeutic decisions. [33, 38, 39, 40]. In 2012, the US Congress re-authorized the FDA to test new drugs in newborns [43]. This decision is an important step in expanding the evidence base for any drug used to treat children. In order to make changes to the medication instructions, it is necessary to have sufficient evidence of the use of the drug in a particular age group of patients. That is why the number of clinical trials in children in the United States from 2002 to 2012 exceeded the number of similar clinical trials in the previous 50 years. Consequently, pediatricians in the United States are not prohibited from prescribing an off-label drug if approved for use FDA [33].

American Academy of Pediatrics (AAP) when analyzing the use of off label drugs in children, she found that at least 50 % of them include special instructions for rational use in pediatrics. However, pediatricians, guided by their clinical experience, must make their own decisions about the appropriate prescription of drugs approved for use in adult patients. This is due to the fact that for the pharmacotherapy of the national maturation of organs, especially the liver and kidneys, as well as changes in metabolism depending on age, which affect the metabolism of the drug.

In 2014, AAP Chairperson Kathleen Neville stated in her guidelines: "Pediatricians should prescribe off label drugs simply because the vast majority of much needed drugs still lack any information in the pediatric label. This is especially problematic for premature infants and infants with chronic or rare diseases." [19]. According to the AAP, off label therapy in children does not involve inappropriate or experimental drug use. Pediatricians who worry about children can make therapeutic decisions about off label drugs based on expert opinion or evidence of their use in a different age group. At the same time, the Academy recommends that pediatricians require pharmaceutical companies to conduct preclinical and clinical trials of drugs in children. In addition, he believes that health insurance companies should not use the instruction as the only criterion for determining the correct tactics of treating children and in which case this treatment is justified. In addition, the practice of treating with cheaper drugs that are used for adults should not automatically be considered first-line therapy in children. The academy also recommends the creation and implementation of a joint (universal) pediatric electronic base of off label drugs used, since the real background information of postmarketing studies in pediatrics on the positive experience of off label drugs and the potential adverse outcomes of such use is very limited.

During the analysis of the practical application of the pediatric nomenclature of drugs, it was found that the rates of their off label prescription vary depending on the pharmacotherapeutic group. Therefore, recommendations are also given to pediatricians to use publications on the study of off label drugs in children. In addition, the AAP encourages pediatricians to speak at conferences on off-label drug use in pediatrics and supports publication of its results in academic journals, including those describing negative results.

In 1997, one of the most significant developments in American medicine was the development and implementation of a series of legislation to modernize the FDA, which lifted the categorical ban on the use of off-label drugs and allowed manufacturers to provide doctors with publications about it, which was the first step in the legal recognition of the use of off-label drugs. Under this law, doctors are allowed to prescribe drugs off label, but pharmaceutical companies are prohibited from advertising unapproved "add-ons" for their drugs. The practice of prescribing drugs off label in pediatrics is now widespread, despite the attendant risks for children and doctors. Therefore, today is the time for strict regulation of the study of drugs that are used off label in children, in order to ensure the safety and efficacy of their pharmacotherapy.

The use of off label drugs in children is a complex and controversial issue due to the high risk of PD. A study in England showed that PR in hospitalized children was more frequently associated with off-label use than licensed use (6% versus 3.9%). This

necessitates taking additional measures to improve the rational use of off label drugs in children. [22].

For many decades, a doctor could prescribe a drug based only on his own professional experience and instructions, without thinking about the laws of health insurance companies. Today, in European countries, treatment with expensive off label drugs is not paid through the health insurance system. The first precedent arose in France, when a child with endocrine pathology was prescribed a drug not registered in the country, and his parents, having applied to a health insurance company to reimburse its cost, were refused. A lengthy legal battle ensued, as a result of which, in France and Germany, doctors in certain emergencies were allowed to prescribe drugs off label. However, at the same time, they bear full legal responsibility if the patient's health is damaged as a result of the treatment. [2, 9, 15, 30, 32, 45].

Changing the route of administration or dosage of off label drugs in children increases the risks associated with their use, but is nevertheless often justified and necessary. Therefore, from a legal and ethical point of view, the use of drugs outside approved indications in pediatrics represents a delicate balance between the attempt by the regulatory authorities to protect patients from dangerous or ineffective drugs, on the one hand, and the doctor's prerogative to apply their professional knowledge and experience to treat the patient, on the other.

A vivid example of the competent attitude of regulatory bodies to the use of off label drugs is the position of the FDA in the United States: if the efficacy and safety of an off label drug has been proven, its manufacturer will agree with the FDA on the possibility of including a certain dosage, route of administration and other necessary new information [91].

Health Canada has mandated regulatory authorities to ensure targeted and rigorous monitoring of off label drug use, especially for vulnerable populations such as children, pregnant women and the elderly. In particular, increased attention is paid to the use of antipsychotic drugs and antidepressants in children. The Canadian Pediatric Society plays an important role in addressing this issue with an off label drug monitoring program [10].

In the UK, doctors are also allowed to prescribe off label drugs. Thus, the British General Medical Council authorized the prescription of drugs off label, provided that they are indicated more than alternative ones, and also have sufficient evidence of safety and efficacy. At the same time, special attention is paid to the dosage of drugs, which potentially exposes patients to the risk of PD and can harm the therapeutic effect. For the rational use of off label drugs in pediatrics in the UK, it is necessary to subsequently conduct their clinical trials for authorization and detailed informing doctors and parents about the use of off label drugs [17].

Currently, in European and other countries, only about 35% of drugs on the pharmaceutical market are approved for use in children. A similar situation is observed in the United States, where the FDA approved only 20-30% of drugs for children. In 2010, when conducting a comprehensive multicenter clinical study on the use of off label drugs in pediatric practice in the EU, which covered 30 countries (27 of them are EU members), their frequent use in the age group from 0 to 28 days was established, as well as in children under 2 years of age.

However, it should be noted that the national ministries and departments of health of the EU countries individually approach the use of off label drugs, since each state has its own characteristics in the field of drug circulation, including the rules for insurance of treatment, which is an important issue in the use of off label therapy in children [91].

In India, the number of off label drugs prescribed to pediatric inpatients is significantly higher than in other countries. The share of nationally prescribed off label drugs in India for patients aged 0 to 12 admitted to hospital is 70%. These are drugs that are prescribed for respiratory diseases (82%), for the treatment of pathologies of the nervous system (53%) and antibacterial agents (73%). In 2011, patients included in the study (97%) received at least one off label drug.

The most common reason for off label prescribing (63%) is the use of drugs in pediatric patients at higher doses (ceftriaxone, amikacin, paracetamol)

[92, 47]. In Russia, the use of off label drugs in children is carried out in the case of:

- ✓ the presence of a serious illness that threatens life or for a long time disrupts the quality of life;
- ✓ the absence in the age group of drugs registered according to indications for the treatment of this disease;
- ✓ there is scientific evidence of a curative or palliative effect with this drug.

In 2006, WHO and the United Nations Children's Fund (UNICEF), acting under the auspices of the United Nations, held consultations in Geneva on the range of essential drugs for children, where they identified ways to eliminate the problems of pharmacotherapy when using off- label drugs in children, considered a draft work plan for WHO and UNICEF for the program "Best Medicines for Children" and discussed the suitability of existing regulatory guidelines for the safety of treatment for children. In 2007, WHO adopted a resolution on the Best Medicines for Children program to improve monitoring of the safety of off-label medicines in different age groups of children.

In the same year, the 60th session of the World Health Assembly reviewed a report prepared by WHO on medicines for children and adopted a resolution approving specific actions by WHO and EU Member States to address contemporary problems in prescribing medicines for children, including those used off label. In December 2007, WHO promulgated a directive according to which it is necessary to "introduce drugs according to the age of the child" in order to ensure the correct use of the optimal dose and route of administration of the drug in children. International organizations, EU governments, the pharmaceutical industry, researchers, healthcare providers, professional associations, academia and civil society have supported this initiative. For example, the EU has approved conditions on how to submit available data on drugs that are used off label for "conditional approval" ahead of schedule. [32].

Thus, conditions are created for European pharmaceutical companies to expand the use of off label drugs. At the same time, there are no specific approving documents that would directly legalize their off label use in pediatrics.

WHO currently believes that the situation of off-label drug use in children can be improved by educating physicians about such experiences in pediatrics in the form of scientific articles or discussions at scientific conferences. The physician should be familiar with the latest data on the use of drugs off label, published both in the collections of clinical pharmacology and in other sources. Only such targeted and coordinated action can ensure the realization of children's right to a safe, economically acceptable and therapeutically effective off label medicine [23].

Thus, ideal off-label pediatric pharmacotherapy is still a global challenge for regulators and physicians. Children are sometimes prescribed off label drugs when there is insufficient evidence, when the drugs used are outside the licensor's limits in terms of dose, route of administration, indication or age. Therefore, this use of drugs poses a risk of unexpected adverse health effects in children. When using off label drugs in children, it is necessary to remember that a child is not a "little adult" and take into account:

- ✓ features of metabolism and physiological processes of the child's body;
- ✓ features and unpredictable changes in the pharmacodynamics and pharmacokinetics of drugs in the child's body;
- ✓ features of the child's psyche (compliance, the "placebo" effect, psychology, etc.).

Among the problems of off label therapy in pediatrics, a perennial problem around the world is the lack of specific recommendations for the use of drugs for neonatal patients. With the adoption by WHO of a resolution on pediatric patients in 2007, tangible steps have been taken in Europe to increase clinical trials in pediatrics. Currently, very few clinical trials include newborns who are still therapeutic orphans, as the attitude towards the drugs intended for them has not changed dramatically so far. This is because the therapeutic indications are unique for this patient population and the number of drugs required is relatively small. In addition, pharmaceutical companies have very little incentive to develop drugs and recommend dosage for children of this age, because the required research is specific, unconventional and expensive. The difficulty of pharmaceutical companies in the development of drugs for

newborns also stems from the reluctance of parents to give permission for trials on their children. Lack of approval for the use of off label drugs in neonates does not mean that the drug is contraindicated, but only indicates that the risks or benefits for a particular patient population have not been considered. This creates an ethical dilemma for the physician, who has the ability to either deprive newborns of potential therapeutic care due to the lack of alternatives, or to use the drug off label, despite the lack of licensing, based on available clinical experience [43].

EMA identified clinical trials in children as high priority. The EMA has approved a list of priority drugs for use in various pediatric age groups, which is updated every year. In addition, there are EU funding projects under the Joint Infections in Newborns program to evaluate the antibacterial drugs on the priority list EMA.

Consequently, the known data on off-label prescribing in children varies greatly from study to study due to differences in definitions of off-label: methodology, sample size, study population (age range), number of drugs considered, and medical care settings (for example, inpatient or ambulatory treatment).

High rates of off label use of pediatric drugs were noted in inpatient settings (36-92%), especially in newborns (80-97%), while the vast majority of children receive drugs on an outpatient basis [43, 76]. Although the use of off label drugs is widespread in pediatrics, it is not always proven. For example, off label prescriptions have actually been supported by high quality data for glucocorticoids and for vomiting ondansetron.

In Italy, two new laws were published, which introduced norms for the authorization of clinical trials of drugs in the pediatric population, but in the first three years in newborns, they accounted for only 1% of all clinical trials. In 2010, the working group on pediatrics prepared a list of drugs that were used off label, which is supported by scientific evidence. In May 2014, members of this group carried out an information campaign called "Medicines and Pediatrics". These were encouraging steps in this regard, as evidenced by the emergence of new and off label drugs for newborns in recent years. [67, 90, 98].

An analysis of the FDA database from 1997 to 2010 showed that of the 28 drugs studied in 41 different studies, there were also drugs for newborns. As a result, 24 drugs were approved for use in newborns. However, such research is still limited in neonatology [16].

The study, published in 2019 in the American Journal of Pediatrics, analyzed data collected from 2006 to 2015, which provides information on the frequency, trend and reasons for prescribing off label drugs by doctors to children under 18 years of age. This is the first study in a decade to look at how American doctors prescribe a wide range of off label drugs not meant for children. The US National Outpatient Care Survey, conducted between 2006 and 2015, found that in 44.5% of visits, private physicians prescribed off-label drugs to children that were beyond the approved age, weight, dose, route of administration, or indications. to use.

The study found that in about 19% of visits, pediatricians prescribed one or more off label systemic drugs, often to treat common conditions such as respiratory infections [50, 59], asthma or mental health problems. Doctors prescribed drugs off label to about 83% of newborns, 49% of infants, and about 40% of other ages. It was also shown that off label prescriptions increased from 42% in 2006 to 47% in 2015. Off label prescription rates were higher for girls and for children with chronic conditions. Specialists prescribed them more often than general practitioners. There were more off label prescriptions for gastrointestinal disorders in younger age groups and for mental disorders in older age groups. [6, 35, 58, 85].

Consequently, from the above analysis, it can be seen that progress in the use of off label medicines for newborns has been made since the adoption of the EU resolution in 2007. The 10-year period may have been too short for significant change, especially for preterm infants, whose survival rates have increased significantly in recent years. However, the existing legislation regulating the use of off label drugs in pediatrics is still too weak to meet the existing clinical needs. Therefore, newborns, which represent the most vulnerable child subpopulation, remain a group of patients with limited access to evidence-based therapy. This leads to an increased risk of AR and medication errors, as well as to a high degree of instability in the results of

the use of off label drugs observed in different countries. There is still insufficient evidence of the safety and efficacy of drugs when administered off label to newborns, since treatment outcomes are often extrapolated from adult patients to children, and pharmacotherapy in the neonatal age group is not always studied in clinical trials. Therefore, whenever possible, neonatal medications should be used in accordance with approved indications to ensure, on the one hand, they are protected from potential risks, and on the other hand, this category of patients should not be deprived of a useful alternative in the form of off label drugs when treatment with licensed drugs is not possible. Off-label drug use is neither experiment nor drug research; it must be based on sound scientific knowledge. The healthcare legal framework obliges drug manufacturers to conduct clinical trials in children if the drug is intended for subsequent use in this category of patients. Children have the right to receive safe and effective medicines with the appropriate level of evidence, at the appropriate dose, and with a specific route of administration for approved indications. Only close collaboration between all those involved in neonatal drug use will ensure that these patients are not left as therapeutic orphans.

Off label use of drugs is associated with a significant risk of adverse reactions in children [70, 75, 79, 84, 93]. Severely ill newborns and infants are more vulnerable to the development of dangerous ARs. Therefore, there is a need for more clinical trials in pediatrics, as well as post-marketing observations of the effectiveness of the studied drugs. Problems associated with the use of off label drugs should be documented at all times. For "traditional", long-standing off label drugs, additional clinical trials and licensing for new indications will also need to be conducted to make these drugs safer for children.

Consequently, the use of off label drugs in pediatric practice remains an urgent global problem in medicine. Progress in the treatment of children cannot be achieved without controlled clinical trials to study the efficacy and safety of drugs used in pediatrics. Today, the expansion of indications and age ranges, the analysis of new dosage regimens and routes of drug administration in children should be considered as one of the priority areas of activity of practical medicine and pharmaceutical companies. An important condition for conducting clinical trials in children is their strict compliance with international requirements. It is also necessary to improve the implementation of pharmacovigilance in the control of the use of off label drugs in children. Practitioners can make a significant contribution to solving this problem by timely informing pharmacovigilance authorities about the PR of medicines in pediatrics. When deciding to prescribe an off label drug to a child, the doctor must be sure that this is the only correct step, provided that there is a state formulary of drugs and a national list of essential drugs for children. Physicians must make their decisions based on reliable data based on factual information about the effectiveness and safety of drugs for a specific pathology. In any case, one should remember and follow the key principle of medicine - primum non nocere.

Most of the pediatric off label drug use data comes from clinical trials in adult patients, but full extrapolation of this data to children is not correct. A growing organism differs from an adult in the state of the receptor apparatus, the mechanisms of absorption, biotransformation, excretion processes, the qualitative and quantitative composition of the protein fractions of blood plasma, etc. This not only changes the pharmacodynamics and pharmacokinetics of the drug, but also determines the characteristics of the use of drugs in children. Moreover, the drugs can specifically affect the physical and cognitive development of the child, bone tissue, immune and puberty. All these facts require clinical trials of drugs with the participation of children as subjects, however, the frequency of such trials remains low (sometimes for objective reasons). That is why at this time the question of the high frequency of off label drug use in children remains very relevant in medicine.

## References

1. Aagaard L. Off-label and unlicensed prescribing of medicines in pediatricn populations: occurrence and safety aspects // Basic. Clin. Pharmacol. Toxicol. – 2015. – Vol. 117, N 4. – P. 215–218/

2. Ach T. Off-label und Arzneimittelzulassung: eine (un) mögliche Kombination // Schriften der Wissenschaftlichen Hochschule Lahr. – 2010. – Vol. 22. – P. 16–36. 21. Achar J., Hewison C., Cavalheiro A. P.et al. Off-label use of bedaquiline in children and adolescents with multidrug-resistant tuberculosis // Emerg. Infect. Dis. – 2017. – Vol. 23, N 10. – P. 1711–1713.
3. Balan S, Hassali MAA, Mak VSL. Two decades of off-label prescribing in children: a literature review. World J Pediatr. 2018 Dec;14(6):528-540. doi: 10.1007/s12519-018-0186-y. Epub 2018 Sep 14. PMID: 30218415.
4. Ballard C. D., Paterson G. M., Thompson A. J. et al. Off-label use of medicines in pediatric inpatients at an Australian teaching hospital // J. Paediatr. Child. Health. – 2012. – Vol. 49. – P. 38–42.
5. Barrington K. J., Finer N. Inhaled nitric oxide for respiratory failure in preterm infans // Cochrane Database Syst. Rev. – 2010. – Vol. 12. – P. 8–12.
6. Bellis J. R., Kirkham J. J., Anthony J. N. et al. Adverse drug reactions and off label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to pediatric hospital // Br. J. Clin. Pharmacol. – 2014. – Vol. 77. – P. 545–553.
7. Bevacqua M, Baldo F, Pastore S, Valencic E, Tommasini A, Maestro A, Rabusin M, Arbo A, Barbi E. Off-Label Use of Sirolimus and Everolimus in a Pediatric Center: A Case Series and Review of the Literature. Paediatr Drugs. 2019 Jun;21(3):185-193. doi: 10.1007/s40272-019-00337-7. PMID: 31124053.
8. Blanco-Reina E., Vega-Jiménez M. A., Ocaña-Riola R. et al. Estudio de las
prescripciones farmacológicas en niños a nivel de atención primaria: evaluación
de los usos off-label o fuera de ficha técnica // Aten. Primaria. – 2015. – Vol. 47,
N 6. – P. 344–350.
9. Brennan Z. French pathway for off label prescribing increases scrutiny, while allowing access // International Pharmaceutical Regulatory Monitor. – 2012. – Vol. 40 (Iss.11). – P. 7-12.
10. 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.
11. Burch S., Griffin S., Walker S. et al. Omalizumab for the treatment of severe persistent allergic asthma in children aged 6–11 years: a NICE single technology appraisal // Pharmacoeconomics. – 2012. – Vol. 30 (Iss. 11). – P. 991–1004.
12. Casañ V. A., Escribano B. C., Garrido-Corro B. et al. Off-label and unlicensed drug use in a Spanish Neonatal Intensive Care Unit // Farm. Hosp. – 2017. – Vol. 41, N 3. – P. 371–381.
13. Causes and legal aspects of 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
14. Celegari L. H., Ebone P., Tonelli T. S. et al. The Unlicensed and Off-label Prescription of Medications in General Paediatric Ward: An Observational Study // Current. Pediatric Reviews. – 2019. – Vol. 15 (Iss. 1). – P. 62–66.
15. Chalumeau M., Salanave B., Assathiany R. et al. Off label and unlicensed drug use among French office based paediatricians // Arch. Dis. Child. – 2000. – Vol. 83. – P. 502–505.
16. Chen D. T., Wynia M. K., Moloney R. M. et al. U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: Results of a national survey // Pharmacoepidemiol. Drug. Saf. – 2009. – Vol. 18, N 11. – P. 1094–1100.
17. 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.
18. Choonara I., Conroy S. Unlicensed and off-label drug use in children: Implications for safety // Drug. SafInt. J. Med. Toxicol. Drug. Exp. – 2002. – Vol. 25, N 1. – P. 1–5.
19. Christine Allen H., Connor Garbe M., Lees Julie, Aziz Naila et al. Off-label
Medication Use in Children, More Common Than We Think: A Systematic Review
of the Literature // J. Okla State Med. Assoc. – 2018. – Vol. 111 (Iss. 8). – P. 776–783.

20. Chua K. P., Fischer M. A., Linder J. A. Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study // BMJ. – 2019. – Vol. 16. – P. 364: k5092. doi: 10.1136/bmj.k5092.
21. Clark R. H., Kueser T. J., Huckaby W. M. et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group // N. Engl. J. Med. – 2000. – Vol. 342. – P. 469–474.
22. Conroy S., Impicciatore P., Knoeppel C. et al. Survey of unlicensed and off label drug use in pediatric wards in European countries. European Network for Drug Investigation in Children // BMJ. – 2000. – Vol. 320 (Iss. 7227). – P. 79–82.
23. Dal Pan G. J. WHO Drug Information: Monitoring the safety of off-label medicine use // WHO Drug Information. – 2009. – Vol. 23 (Iss. 1). – P. 21–22.
24. Dani C., Bertini G., Pezzati M. et al. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome // Acta Paediatr. – 2006. – Vol. 95 (Iss. 9). – P. 1116–1123.
25. De Zen L., Marchetti F., Barbi E., Benini F. Off-label drugs use in pediatric palliative care // Ital. J. Pediatr. – 2018. – Vol. 44. – P. 1–6.
26. Dennis M. US reviewing atypical antipsychotic use in children: Report. (2013). Availableat: http: // www.firstwordpharma.com/node/1130783
27. Ditsch N., Kumper C., Summerer-Moustaki M. et al. Off-label use in Germany – A current appraisal of gynaecologic university departments // Eur. J. Med. Res. – 2011. – Vol. 16, N 1. – P. 7–12.
28. Dooms M., Cassiman D., Simoens S. Off-label Use of Orphan Medicinal Products: a Belgian Qualitative Study // Orphanet J. of Rare Diseases. – 2016. – Vol. 11, N 1. – P. 1–44.
29. Dooms M., Killick J. Off-label use of Medicines: the need for good practice
guidelines // International J. of Safety in Med. – 2017. – Vol. 29, N 1– 2. – P. 17–23.
30. 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.
31. Emmerich J., Dumarcet N., Lorence A. France's new framework for regulating off label drug use // N. Engl. J. Med. – 2012. – Vol. 367, N 14. – P. 1279–1281.
32. European Commission. State of pediatric medicines in the EU: 10 years of
the EU Pediatric Regulation. 2017. – https://ec.europa.eu/health/sites/health/files/
files/paediatrics/docs/2017_childrensmedicines_report_en.pdf
33. Fairman K. A., Curtiss F. R. Regulatory actions on the off label use of prescription drugs: Ongoing controversy and contradiction in 2009 and 2010 // J. Manag. Care Pharm. – 2010. – Vol. 16, N 8. – P. 629–639.
34. FDA, Guidance for Industry Distributing Scientific and Medical Publications
on Unapproved New Uses-Recommended Practices. – 2014 p.
35. Frattarelli D. A., Galinkin J. L., Green T. P. et al. Policy Statement on the off label use of drugs in children // Pediatrics. – 2014. – Vol. 133 (Iss. 3). – P. 563–568.
36. Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, Van Den Anker JN; American Academy of Pediatrics Committee on Drugs. Off-label use of drugs in children. Pediatrics. 2014 Mar;133(3):563-7. doi: 10.1542/peds.2013-4060. Epub 2014 Feb 24. PMID: 24567009.
37. 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.
38. Freund M. On-Label – Off-label: Gibt es eine Sicherheitsgarantie durch Regulation? // GGW. – 2006. – Vol. 4. – P. 22–31.
39. Fugh-Berman A., Melnick D. Off-label promotion, On-Target Sales // PLoS Med. – 2008. – Vol. 5 (Iss. 10). – P. 1432–1435.
40. Gazarian M., Kelly M., McPhee J. R. et al. Off-label use of medicines: Consensus recommendations for evaluating appropriateness // Med. J. Aust. 2006. Vol. 185, N 1.
https://www.mja.com.au/journal/2006/185/10/labelusemedicines-consensus-recommendations-evaluating-appropriateness
41. General Medical Council. Good practice in prescribing and managing medicines and devices.

General Medical Council. – 2013. – http: // www.gmc-uk.
org/Prescribing_Guidance_2013_50955425.pdf.
42. Gonçalves A. C. de S., Reis A. M. M., Marçal A. C. G., Bouzada M. C. F.
Use of unlicensed and off-label drugs in neonates in a Brazilian university hospital
// Brazilian J. Pharm. Sci. – 2018. – Vol. 53, N 3. – P. 1–10.
43. HalineTereza Matias de Lima Costa, Tatiana Xavier Costa, Rand Randall Martinset al. Use of Off-Label and Unlicensed Medicines in Neonatal Intensive Care // PLoS One. – 2018. – Vol. 13 (Iss. 9). – P. 1–12.
44. Hsiao Hsiu-Feng, Yang Mei-Chin, Lai Mei-Yin et al. The Off-Label Use of Inhaled Nitric Oxide as a Rescue Therapy in Neonates With Refractory Hypoxemic Respiratory Failure: Therapeutic Response and Risk Factors for Mortality // J. of Clin. Med. – 2019. – Vol. 8 (Iss. 8). – P. 1–10.
45. Huber M., Andersohn F., Sarganas G. et al. Metamizole-induced agranulocytosis revisited: results from the prospective Berlin Case-Control Surveillance Study // Eur. J. Clin. Pharmacol. – 2015. – Vol. 71. – P. 219– 227.
46. Igelman S, Kurta AO, Sheikh U, McWilliams A, Armbrecht E, Jackson Cullison SR, Kress DW, Smith A, Castelo-Soccio L, Treat J, Boothe WD, Diaz LZ, Levy ML, Patel A, Lee LW, Fraile-Alonso MC, Antaya RJ, Shah S, Kittler N, Arkin L, Siegfried E. Off-label use of dupilumab for pediatric patients with atopic dermatitis: A multicenter retrospective review. J Am Acad Dermatol. 2020 Feb;82(2):407-411. doi: 10.1016/j.jaad.2019.10.010. Epub 2019 Oct 10. PMID: 31606479.
47. Jain S. B., Bavdekar S. B., Gogtay N. J. et al. Off label drug use in children // Indian. J. Pediatr. – 2008. – Vol. 75. – P. 1133–1136.
48. Jansen R. The off label use of medication in South Africa – what about some information for medical practitioners? // SAMJ. – 2009. – Vol. 99 (Iss. 6). – P. 438–439.
49. Jobe AH. Off-Label Drugs in Neonatology: Analyses Using Large Data Bases. J Pediatr. 2019 May;208:9-11. doi: 10.1016/j.jpeds.2019.01.038. Epub 2019 Feb 26. PMID: 30824166.
50. Jong G. W., Eland I. A., Strickerf B. H. C. et al. Unlicensed and off label prescription of respiratory drugs to children // Eur. Respir. J. – 2004. – Vol. 23, N 2. – P. 310–313.
51. Karesh A, Tomaino J, Mulberg AE. Off-label use of medicine in pediatrics: focus on gastrointestinal diseases. Curr Opin Pediatr. 2013 Oct;25(5):612-7. doi: 10.1097/MOP.0b013e328363ed4e. PMID: 23995427.
52. Khdour M. R., Hallak H. O., Hawwa A. F. et al. Extent and nature of unlicensed and off label medicine use in hospitalized children in Palestine // Int. J. Clin. Pharm. – 2011. – Vol. 33, N 4. – P. 650–655.
53. Kieran E. A., O'Callaghan N., O'Donnell C. P. Unlicensed and off label drug use in an Irish neonatal intensive care unit: a prospective cohort study // Acta Pediatric. – 2014. – Vol. 103. – P. 139–142.
54. Kimland E., Odlind V. Off-label Drug Use in Pediatric Patients // Clinical. Pharmacology & Therapeutics. – 2012. – Vol. 91 (Iss. 5). – P. 796–801.
55. Kontou A., Sarafidis K., Roilides E. Antimicrobial dosing in neonates // Expert
Rev. Clin. Pharmacol. – 2017. – Vol. 10. – P. 239–242.
56. Kouti L., Aletayeb M., Aletayeb S. M. H., Hardani A. K., Eslami K. Pattern and extent of off-label and unlicensed drug use in neonatal intensive care units in Iran // BMC Pediatrics. – 2019. – Vol. 19 (Iss. 3). – P. 1–7.
57. Krajnović D, Ubavić S, Bogavac-Stanojević N. Pharmacotherapy Literacy and Parental Practice in Use of Over-the-Counter Pediatric Medicines. Medicina (Kaunas). 2019 Mar 26;55(3):80. doi: 10.3390/medicina55030080. PMID: 30917624; PMCID: PMC6473441.
58. Krishnan D., Ongso Y., Leknys M. Misoprostol, for postpartum baemorrhage in the Australian bush // Aust. Fam. Physician. – 2014. – Vol. 43. – P. 569–570.
59. Krystal J. H., Rosenheck R. A., Cramer J. A. et al. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service–related PTSD: A randomized trial // JAMA. – 2011. – Vol. 306, N 5. – P. 493–502.
60. Kumar P. Committee on Fetus and Newborn. American Akademy of Pediatrics. Use of inhaled nitric oxide in preterm infants // Pediatrics. – 2014. – Vol. 133 (Iss. 1). – P. 164–170.

61. Landwehr Caitlin, Richardson Jennifer, Bint Lewis et al. Cross-sectional Survey of off-label and Unlicensed Prescribing for Inpatients at a Paediatric Teaching Hospital in Western Australia // PLoS One. – 2019. – Vol. 14 (Iss. 1). – P. 1–12.
62. Laughon M. M., Capparelli E. V., Kearns L. G. et al. Innovative clinical trial design for pediatric therapeutics // Expert. Rev.Clin. Pharmacol. – 2011. – Vol. 4. – P. 643–652.
63. Lee J. L., Redzuan A. M., Shah N. M. Unlicensed and off label use of medicines in children admitted to the intensive care units of a hospital in Malaysia // Int. J. Clin. Pharm. – 2013. – Vol. 35. – P. 1025–1029.
64. Lindell-Osuagwu L., Minna Helin-Tanninen, H. Kokki et al. Off-label and unlicensed drug prescribing in three pediatric wards in Finland and review of the international literature // J. Clin. Pharm.Ther. – 2009. – Vol. 34 (Iss. 3). – P. 277–287.
65. Liu L. Hong-Yu Yang, Yan Lou et al. Off-label prescriptions in intensive care unit: the Chinese experience // Therapeutics and Clin. Risk Management. – 2018. – Vol. 14. – P. 195–202.
66. Magalhães J., Rodrigues A. T., Roque F. et al. Use of off-label and unlicenced drugs in hospitalisedpaediatric patients: a systematic review // Eur. J. Clin. Pharmacol. – 2015. – Vol. 71, N 1. – P. 1–13.
67. Maratea D., Bettio M., Corti M. G. et al. The efficacy and safety of rituximab in treating childhood nephrotic syndrome: an Italian perspective // Ital. J. Pediatr. – 2016. – Vol. 42 (Iss. 1). – P. 1–3.
68. Marc Ellsworth A., Harris M. N., Carey W. A. et al. Off-label use of inhaled nitric oxide after release of NIH consensus statement // Pediatrics. – 2015. – P. 643–648.
69. Mario Miriam, Katia M. C. Verhamme, Alfedo Nicolosi et al. Drug use in children: cohort study in three European countries // Brit. Med. J. – 2008. – Vol. 337. – P. 1–13.
70. Mason J., Pirmohamed M., Nunn T. Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature // Eur. J. of Clin. Pharmacol. – 2012. – Vol. 68 (Iss. 1). – P. 21–28.
71. 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.
72. Mühlbauer B., Janhsen K., Pinchler J. et al. Off-label use of prescription drugs in childhood and adolescence: an analysis of prescription patterns in Germany // Dtsch. Arztebl. Int. – 2009. – Vol. 106. – P. 25–31.
73. Mulligan E., Messenger H. Mifepristone in South Australia – the first 1343 tablets // Aust. Fam. Physician. – 2011. – Vol. 40. – P. 342–345.
74. Neubert A., Felisi M., Bonifazi A. et al. Off-label and unlicensed use of medicines for children // Pharmaceut. Policy Law. – 2009. – Vol. 11. – P. 41–49.
75. Othman Khaled M Said, Abdeltawab A. A., Yosef A. E. et al. Safety and efficacy of off-label use of ivabradine in patients with acute heart failure // J. of the Saudi Heart Association. – 2019. – Vol 31 (Iss. 4). – P. 179–187.
76. Palmaro A., Bissuel R., Renaud N. et al. Off-label prescribing in pediatric outpatients // Pediatrics. – 2015. – Vol. 135, N 1. – P. 49–58.
77. 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.
78. 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.
79. Ribeiro M., Jorge A., Macedo A. F. Off-label drug prescribing in a Portuguese paediatric emergency unit // Int. J. Clin. Pharm. – 2013. – Vol. 35 (Iss. 1). – P. 30–36.
80. Rite-Gracia S, Avila-Alvarez A. Medicamentos off-label y sin licencia en neonatología. An Pediatr (Engl Ed). 2021 Mar;94(3):127-128. doi: 10.1016/j.anpedi.2020.12.011. Epub 2021 Jan 19. PMID: 33483240.
81. Roberts G., Xatzipsalti M., Borrego L. M. et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical

Immunology // Alergy. – 2013. – Vol. 68 (Iss. 9). – P. 1102–1116.
82. 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.
Saf. – 2011. – Vol. 20, N 5. – P. 474–481.
83. Santos D. B., Clavenna A., Bonati M. et al. Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil // Eur. J. Clin. Pharmacol. – 2008. – Vol. 64 (Iss. 11). – P. 1111–1118.
84. Shah S. S., Hall M., Goodman D. M. et al. Off label drug use in hospitalized children // Arch. Pediatr. Adolesc. Med. – 2007. – Vol. 161. – P. 282–290.
85. Simsek M., Verschuren S., Hoentjen F. et al. Off-label Prescriptions of Drugs Used for the Treatment of Crohn's Disease or Ulcerative Colitis // Alimentary Pharmacology and Therapeutics. – 2019. – Vol. 49 (Iss. 10). – P. 1293–1300.
86. Smyth A. R., Barbato A., Beydon N. et al. Respiratory medicines for children: Current evidence, unlicensed use and research priorities // Eur. Respir. J. – 2010. – Vol. 35, N 2. – P. 247–265.
87. Sohn M., Moga D. C., Blumenschein K., Talbert J. National trends in offlabel use of atypical antipsychotics in children and adolescents in the United States // Med. (United States). – 2016. – Vol. 95 (Issue 23). – P. e3784. doi: 10.1097/MD.0000000000003784
88. Stafford R. S. Off-label use of drugs and medical devices: A review of policy implications // Clin. Pharmacol. Ther. – 2012. – Vol. 91, N 5. – P. 920–925.
89. Stephanie M. Greence, Lars Noah, Debate, Off-label Drug Promotion and the First Amendment. – 2014. – P. 162.
90. Sturkenboom M., Felisi M., Manfredi C. et al. Pediatric status and off label use of drugs in children in Italy, United Kingdom and the Netherlands // Pharmaceut. Policy Law. – 2009. – Vol. 11. – P. 51–59.
91. Tabarrok A. T. Assessing the FDA via the anomaly of off label drug // Independant Review. – 2000. – Vol. 5 (Iss. 1). – P. 25–53.
92. The Indian Medical Council Act (act. № 102 of 1956). – http://legislative.gov.in/sites/default/files/A1956-102_0.pdf
93. Turner S., Nunn A. J., Fielding K. et al. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: A prospective study // Acta Paediatr. – 1999. – Vol. 88, N 9. – P. 965–968.
unlicensed medicines in children // J. Korean. Med. Sci. – 2018. – Vol. 33, N 37: –
94. Unni JC, Joseph RB. Off-Label Medications in Pediatrics. Indian J Pediatr. 2019 Dec;86(12):1149. doi: 10.1007/s12098-019-03029-9. Epub 2019 Jul 20. PMID: 31327145.
95. van Wering HM, Tabbers MM, Benninga MA. Are constipation drugs effective and safe to be used in children? A review of the literature. Expert Opin Drug Saf. 2012 Jan;11(1):71-82. doi: 10.1517/14740338.2011.604631. Epub 2011 Jul 29. PMID: 21801036
96. Wertheimer A. Off-label prescribing of drugs for children // Current Drug. Safety. – 2011. – Vol. 6. – P. 46–48.
97. Yackey K, Stukus K, Cohen D, Kline D, Zhao S, Stanley R. Off-label Medication Prescribing Patterns in Pediatrics: An Update. Hosp Pediatr. 2019 Mar;9(3):186-193. doi: 10.1542/hpeds.2018-0168. Epub 2019 Feb 11. PMID: 30745323.
98. Yang C. P., Veltri M. A., Yaster M. et al. US FDA approval for medications used in the pediatric intensive care unit: a continuing conundrum // Pediatr. Crit. Care Med. – 2010. – Vol. 12 (Iss. 5). – P. 195–199.