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CAUSES AND LEGAL ASPECTS OF THE OFF LABEL DRUGS EMERGENCE: literature review

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Abstract

"Off label use" is the use of a medicinal product "beyond the label". The term has a broader meaning: use according to an indication, in a dosage form, dose, or scheme, in a population of patients, information about which is not contained in the approved instructions for the medical use of the drug. Today, in off-label therapy, an important unresolved legal issue remains professional responsibility for the selection and prescription of off-label drugs, since the situation in each country for off-label prescription of drugs is different.

The work aimed to analyze the reasons and legal aspects of the appearance of off-label drugs worldwide.

Materials and methods. Analysis of scientific publications on the Pub Med platform regarding the reasons and legal aspects of the emergence of off-label drugs.

Results and discussion. Off-label therapy is sometimes described as a typical medical practice that, for commercial reasons, is not subject to high-quality clinical trials and subsequent regulatory control, but the absence of the latter does not diminish its importance for pharmacotherapy. The advantages of the off-label therapy method are the shorter implementation time of such a drug and a decrease in costs for its development by about 25% compared to the creation of new on-label drugs by the traditional method. This type of innovation in pharmacy is considered a method of "repurposing" medicine to be. Most doctors, pharmacists, and patients today recognize the principle: it is not important whether the drug is on-label or off-label, but whether it helps the patient to recover.

Conclusions. Thus, there are objective prerequisites for the use of off-label drugs in almost all areas of clinical medicine. However, the optimal approach to this problem is if it is regulated by law.

Keywords: *off label use, on label use, legal aspects of drugs*

Introduction

In the last century, the world has seen an unprecedented increase in life expectancy. Demographic analysts believe that 40% of this longevity in recent decades has been driven by pharmaceutical innovation in the form of new drugs. Much of this pharmaceutical boom is due to the improvements in the treatment of cardiovascular diseases (hypertension, stroke, and myocardial infarction), as well as medicines that affect the causes of other diseases. Thus, in the pharmacotherapy of HIV/AIDS alone, over the past three decades, 30 new drugs have appeared that have prevented what was until recently considered a death sentence or an incurable chronic disease. In addition to saving and prolonging life, these drugs also improved the quality of life, affecting disability in multiple sclerosis or debilitating nausea in cancer chemotherapy [1]. Considering this progress and looking into the future, there are high hopes for the emergence of other new effective drugs for the treatment of cancer, sepsis, hepatitis, and HIV infections.

Today, it takes 10-15 years and costs $ 4-11 billion to create and formally approve a new drug based on a new chemical structure following the requirements of the FDA or other regulatory bodies. However, there is a debate about the reality of these numbers. The pharmaceutical industry believes that this figure includes the cost of the drug and even all of the failed development costs associated with investment returns. In retrospect, they believe that drug design failures could have been avoided [2]. Whereas their opponents argue that the actual costs of creating and approving new drugs by regulatory authorities are significantly (several times) less. Thus, in the field of introducing off-label drugs, pharmaceutical companies have found a way to simultaneously increase the possibilities of existing pharmacotherapy and their income with minimal legal, time, and financial risks [3].

The term "off-label use" means the use of a drug "outside the label". The term has a broader meaning: use according to an indication, in a dosage form, dose, or scheme, in a population of patients, information about which is not contained in the approved Instructions for the Medical Use of the Drug [4, 5].

However, in reality, the cost of creating new drugs has increased significantly in recent years. This is due to several factors: today, some diseases are difficult to treat, so the number of clinical trials proving the effectiveness of new drugs is growing, and similarly requirements for their safety level are increasing, as the number of regulatory requirements of regulatory authorities increases. In this regard, the real estimate of the cost of creating a new drug has now increased so much that many pharmaceutical companies have undergone a large-scale reorganization of the drug creation process [6]. Although there is little scientific evidence for most off-label prescribing, in some cases the benefits are well known and do not keep patients waiting for many years to conduct large-scale assessments of the risk and benefit of off-label prescribing. However, the evidence for the benefits of off-label drugs for some indications is insufficient to characterize their indications as "evidence-based" and there are also safety concerns [7]. Nevertheless, the search for tools to expand the pharmaceutical market through off-label drugs is very attractive [8]. These drugs can be approved for clinical use at a much lower cost than new drugs, which must undergo a full cycle of pharmacological and toxicological tests before embarking on a risky process of clinical trials. Pharmaceutical companies often choose to develop a completely new drug purely because of commercial interest. In the absence of a commercial factor, there is no incentive for companies to invest even in a shortened pharmaceutical process to prove that an existing drug has usefulness beyond its original use.

Methods

Analysis of scientific publications on the Pub Med platform regarding the reasons and legal aspects of the emergence of off-label drugs.

Results and discussion

The off-label use of a drug does not require the same investment of time, money, or the need to expose a manufacturer to the same level of risk as developing a new on-label drug. However, an off-label drug does not always guarantee the same

degree of efficacy and safety for patients as an on-label drug approved by a regulatory authority. Besides, off-label drug marketing can be effective in crowding out of on-label drugs from the pharmaceutical market, since it is easier to convince a doctor than regulatory bodies of the efficacy and safety of off-label drugs, despite the potential harm to the patient.

The FDA recognizes that significant costs and long approval times prevent many manufacturers from using additional indications for their drugs. Consequently, the FDA has issued the FDA Modernization Act (FDAMA) in 1997, which allowed manufacturers to distribute literature and discuss off-label use of their products. However, any reports regarding off-label use must occur following the submission or future submission of an additional application with the FDA for a new off-label indication of the drug. In reality, no additional clinical trials supporting off-label indications (guaranteed by the manufacturer) are likely to be presented to them after the drug has received the off-label status on the market.

Consequently, the introduction of a new pharmaceutical product is an extremely risky, costly, and time-consuming process. An example of this is the search for neurotropic drugs, which was carried out in 1996-2000 by the following companies: Abbott Laboratories, Boots, Eisai, Fujisawa Pharmaceutical (Astellas Pharma), Glaxo Wellcome (GlaxoSmithKline), Janssen, Eli Lilly and Company, Merck, Nycomed, Organon, Otsuka Pharmaceutical, Pfizer, Reckitt & Colman (Reckitt Benckiser), SmithKline Beecham (GlaxoSmithKline), The 3M Company, Xenova, and Zeneca (AstraZeneca). In the period from 2015-2019, all of the listed pharmaceutical companies except three companies (GSK, Pfizer, and Eli Lilly and Company) have abandoned this task [9].

Over time, the overall regulatory framework for pharmaceuticals in developed countries has become more stringent. Currently, to obtain a marketing authorization for a drug, manufacturers must provide a large amount of information on clinical trial results, adverse reactions, manufacturing and quality control processes, and information on how the drug will be marketed.

Today, on-label drugs need to be tested over a long time to prove their safety and efficacy profile, while generic pharmaceuticals or off-label drugs can only undergo bioequivalence testing.

Thus, at present, the creation of pharmaceuticals presents great difficulties for pharmaceutical companies, including high prices and long cycles of introducing innovations in pharmacotherapy. The traditional drug discovery process first requires testing "candidate drugs" on a pharmacological target using large-scale pharmacological screening. As the candidate study process progresses, pharmacological testing becomes more complex in terms of research volume. After a long preclinical study of a "candidate" for drugs in animals, an application is submitted to a regulatory body (FDA or MoH) to begin clinical trials on patients: preliminary testing in a clinic on volunteers (phase I), then testing the future drug on a target population of patients with a specific disease (phase II) and then large-scale randomized double-blind studies are conducted on patients (phase III clinical trial) [1].

Therefore, for a drug to be approved for medical use, a pharmaceutical company must provide a wealth of information proving that the drug is effective and safe. Therefore, the time and financial benefits of off-label drugs outweigh the potential clinical and economic risks compared to an on-label drug approval.

It should also be noted that over the past 20 years, the standard expert review time for the results of all phases of clinical trials required to obtain regulatory approval has decreased by 50%: from 22 to 12 months for most drugs and is about 6 months for drugs that are prescribed for life-threatening conditions or orphan diseases [10, 11]. However, the ratio of "candidate drugs" in Phase I clinical trials versus those that are ultimately approved is 9: 1; that is 9 fail and 1 succeeds in marketing authorization. The overall ratio of approved drugs to Phase I clinical trial candidates is about 1 in 10. With serious pathology, such as oncology, this figure rises to 1 in 20. Moreover, these numbers remain relatively constant over the years [12].

Failures in the pharmaceutical innovation process can lead to a refusal in approval of the "candidate drug", and then the cost of its creation increases many times, especially if these failures occur at the later stages of the study (for example, in the phase

III of clinical trials - extremely expensive and time-consuming). The costs of pharmaceutical companies in this way of developing a new drug amount to hundreds of millions of dollars.

Therefore, today alternative strategies of production and financial models for the production of new pharmaceuticals have been proposed. These models provide much cheaper and faster drug approval by regulatory authorities than the developments presented above because it is possible to use the necessary pharmacological, technological and analytical information obtained from the development of other drugs [9, 13]. This will reduce or eliminate some of the requirements of the regulatory authorities, which makes the project of creating a new drug cheaper because costs can be avoided in the earlier stages of preclinical and clinical trials (phases I and II). However, the risk associated with side effects that can be detected in phase I clinical trials, when the safety of the "candidate" is first tested, increases by 30-40%. Besides, it cannot be stated that the dose required for a new indication will be the same as when the drug was initially used on-label. In practice, the ideal dose of a drug cannot be determined until a dose-response study has been conducted in a Phase II clinical trial.

Therefore, in cases where a known drug is proposed for a radical new use, there are risks, especially if the new off-label indication of the drug involves the use of a new mechanism or the need to use the drug with a better tolerance than initial use [14]. However, an off-label use of a drug significantly reduces the cost of its implementation. Taking this factor into account, it can be assumed that the economic losses associated with the introduction of an off-label drug are significantly less than at the creation of new drugs by the traditional method; moreover, the introduction of an off-label drug is a faster process.

Thus, the advantages of the off-label therapy method lie in the shorter implementation time of such a drug and a decrease in economic costs for its development by about 25% compared to the creation of new drugs on-label by the traditional method. This type of innovation in pharmacy is considered a method of "repurposing" the future medicine.

"Therapeutic shift" (or "indication shift") is the fact that a drug approved for one indication is gradually used (shifted) in a closely related other indication, despite the lack of clear evidence to support the latter use. Thus, it was wrongly assumed that selective serotonin reuptake inhibitors (SSRIs) would be effective in the treatment of adolescent depression because they were effective in adult depression.

In addition to the above risks for the "drug candidate" itself and the huge associated costs, there is another equally important fact that even those drugs that enter the market do not always pay off their investments. The reason is that forecasts for the introduction of a new drug do not always correspond to reality. Of course, there are many examples of mega-blockbusters whose success is enormous. It is these successes, when viewed in retrospect, that define the perception of unwarranted profits in the pharmaceutical industry.

Consequently, one of the ways to solve the problem of matching the costs of creating a new drug and the profit from its introduction can be the search for new indications and other conditions for the use of drugs on-label, as well as the search for doctors who are ready to prescribe them off-label. The main off-label drug strategy is based on obtaining new evidence of their effectiveness for other indications, dosages, routes of administration, but this can be done with much less production and financial costs than is required for traditional on-label registration of a new drug. Besides, first, the great advantage of the off-label drug creation method is that the risks in the search for new drugs can be largely avoided, provided that a physician must be convinced of the need for such off-label drug indications based on positive clinical evidence, and then there is no need for a rigorous and expensive regulatory approval process. Second, commercial success can be achieved much faster and cheaper, without the time and funds expense required to approve on-label drug regulations. Third, even if the initial off-label trials fail, the financial loss will remain less significant than for on-label drugs. At least, this is the proposed strategy and perspective when introducing off-label drugs [15].

There is another cost-effective strategy for repurposing (licensing) off-label drugs from drugs that were originally approved for rare diseases

(orphan drugs). The latter drugs are initially very expensive, as pharmaceutical companies argue that the small sales of orphan drugs should be offset by their high prices [16]. Of course, the price will not come down when the drug is widely used for off-label indications that are much larger than rare diseases. Therefore, in the practice of pharmaceutical marketing, a variant of orphan innovation is sometimes used - this is a therapeutic area in which additional government incentives have been introduced to strengthen commercial incentives in the production of drugs for the treatment of rare diseases. Orphan drug prices are usually high because their market opportunities are considered to be narrow [17]. However, off-label use of orphan drugs can lead to even blockbuster drugs. This is facilitated by the financial gap between the cost of orphan and off-label drugs due to the size of the pharmaceutical market.

In the United States, Congress passed the Orphan Drug Act in 1983 to stimulate industry investment in the treatment of rare diseases that, in the absence of incentives, were not attractive to the pharmaceutical industry. More than 6,000 diseases are indicated for the use of orphan drugs, and the number of patients with orphan diseases is 20 million in the United States and 30 million in Europe. Therefore, orphan drugs have ample opportunities for their use in off-label therapy [18].

As a result of the FDA's Orphan Drug Act since 1983, more than 300 drugs have been approved for the treatment of rare diseases [11]. US law allows for expedited regulatory approval, marketing tax relief protections, and adequate funding for clinical trials of rare disease drugs. The only thing that the FDA prohibits when approving orphan drugs is weakening the basic principles of adequate safety and efficacy assessment when obtaining regulatory approval. This principle is mandatory for the FDA. Once a drug is approved, the great value for an orphan drug is that a generic competitor for this indication cannot be approved for 7 years (normal patent protection can apply). After the appearance of this law in the United States, a similar legislation has been adopted in Europe, Australia, Singapore and Japan, and other countries.

Even though the term “orphan drugs” is associated with rare diseases, these drugs can be an example of a much wider use, which significantly expands access to the pharmaceutical market for such drugs. For example, in 1989, the FDA approved the use of an erythropoietin-stimulating agent (ESA) for anemic patients with end-stage kidney disease. Erythropoietin was first obtained in 1972, and in the early 1980s, Amgen company gave the drug the trade name Epogen.

In addition to using this orphan drug on-label for kidney disease, it was also later approved for the treatment of HIV-related anemia. Both of these indications have been identified as orphan diseases. However, despite limited use in end-stage renal disease (16%), the off-label market for this drug expanded very quickly to reach almost all kidney dialysis patients who required a blood transfusion, and also thanks to television and print advertising that claimed the drug caused "statistically significant improvements in sex life and life satisfaction." This is how Epogen became an extremely profitable off-label drug. In addition to the originally approved use, ESA was subsequently approved for the treatment of patients with a variety of anemias and non-myeloid cancers. It is due to the latter ESA indication, rather than its orphan use, the pharmaceutical company Amgen has earned most of its revenue [19].

Throughout its commercial life, the average dose of this drug has tripled, and, per Amgen's recommendations (from an initial regimen of 3,500 units), the dose has become 10,000 units, and the price of this drug has increased proportionally. However, higher doses of Epogen have begun to raise concerns about its safety [19, 20].

There is also a tragic side to the use of ESA outside of medicine. In the 1980s, Scandinavian and Dutch cyclists gained access to ESA on the black market and used drugs to improve their performance. From 1987 to 1990, about 18 young cyclists died of unknown causes. Although their sudden death was not officially explained, in 1998 the police found hundreds of vials of erythropoietin on a team of cyclists. This scandal made ESA a notorious drug.

Hence, erythropoietin has come a long way from treating life-threatening rare anemia to a long-term decline in its reputation.

ESA is not the only orphan drug sold off-label. The top 100 best-selling drugs in the United States include 12 names approved for one or more orphan

indications [9]. Thus, the degree of use of modafinil as an off-label drug was set at 90%, which corresponds to more than a billion dollars in sales in 2011 in the United States alone. An analysis of the use of modafinil off-label in the period from 2002 to 2009 showed that the number of its prescriptions for narcolepsy, sleep disturbance during shift work, and sleep apnea tripled [21].

ESA and modafinil are two of the many off-label drugs that are used to treat unapproved indications far more often than to treat approved indications.

One of the serious concerns about off-label drug use is that in this situation the drug "falls into the unexplored field" [22]. In the absence of evidence, it is very difficult to determine unequivocally that a drug is effective and safe. This is especially dangerous for the use of off-label drugs in pediatrics, which are only approved for adult patients. A child is not a small adult [23]. Given the anatomical and physiological age characteristics, it is impossible to calculate the child's dose by direct conversion per kilogram of body weight, based on the adult dose. This can dramatically increase the risk of drug toxicity. For example, the off-label use of acetylsalicylic acid as an antipyretic drug for ARVI in children under 15 years of age can lead to the development of life-threatening Reye's syndrome, in which toxic damage to the brain and liver is observed [24].

Therefore, the main problem with off-label drugs is that they do not always have a proper safety and efficacy assessment following the requirements of the GLP and GCP. On the other hand, the main pharmacological value of off-label drugs lies in their necessity for the patient's health. Although there is anecdotal evidence of the benefits of off-label drugs in some indications, the evidence is too weak to be characterized as "evidence-based," and there are significant safety concerns. However, there are many examples of when an off-label drug is safe and effective [25].

Thus, the global trend of extending the life of people by almost 10 years in the last 50 years is to a certain extent associated with progress in the field of pharmacotherapy, as well as with the emergence of new drugs, including an increase in the off-label drug market. Off-label therapy is especially common in pediatrics and geriatrics (since patients under the age of 18 or over 65 are less involved in clinical trials), oncology (where cancer at the last stage requires more risky treatment), and psychiatry. The healthcare and pharmacy professionals must be self-critical and adhere to reality in life, as many doctors and pharmacists believe that some commonly used drugs are officially approved for certain indications, but in fact, they are off-label pharmacotherapy. Today most doctors, pharmacists, and patients recognize the principle: it is not important whether the drug is on label or off label, but whether it helps the patient to recover.

Off-label therapy is sometimes described as a typical medical practice that, for commercial reasons, is not subject to high-quality clinical trials and subsequent regulatory control, but the absence of the latter does not diminish its importance for pharmacotherapy.

Today, in off-label therapy, an important unresolved legal issue remains professional responsibility for the selection and prescription of off-label drugs, since the situation in each country for off-label prescription of drugs is different.

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