

OFF-LABEL USE OF MEDICINAL PRODUCTS – LEGAL RULES AND PRACTICES

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Abstract: The off-label use of medicinal products raises many interpretation-related issues, not only among physicians but also pharmacists and lawyers. The use of drugs in a manner other than that specified in the Summary of Product Characteristics is not regulated by Polish law. The authors' goal is to discuss the topic mainly from the practical perspective, while also considering its theoretical aspects, and to identify systemic solutions to several problems, that are extremely important for the proper functioning of the entire healthcare system. The paper highlights that there is a fine line between experimental medicinal practices and those that are in keeping with current medical knowledge.

Keywords: Off-label drug use, medicinal products, health policy, prescribing, pharmaceuticals

Defining off-label use

The first issue to be considered in the present article is the definition of the term “off-label.” It means the use of a product “for purposes other than those indicated”, thus raising serious interpretation-related concerns, not only among physicians but also pharmacists and lawyers. Apparently, off-label use does not automatically exclude liability. However, it should be noted that the use of a medicinal product for any purposes other than those indicated in the Summary of Product Characteristics (SmPC) has not been expressly defined in Polish

law. This contrasts with, inter alia, solutions applied in the United States, where the Food and Drug Administration (FDA) has considered such therapies to be legal (1), except for so-called controlled substances, including opioids (morphine or fentanyl), which can only be prescribed for registered purposes. In relation to the issue in general, the FDA has issued guidelines for manufacturers of medicinal products (Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and

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Approved or Cleared Medical Devices) (2). In the United Kingdom, both the Medicines Act of 1968 and European legislation allow physicians to use medicinal products and non-registered pharmaceuticals off-label. Guidelines issued by the General Medical Council (GMC), entitled "Good practice in prescribing medicines – guidance for doctors," are currently in force, and they stipulate that physicians must:

- be convinced that off-label use will be more beneficial for the patient than the corresponding licensed therapy;
- be convinced that there is enough evidence and/or experience regarding the use of a given medicinal product, proving both its efficacy and safety;

- take responsibility for the prescribed product, and supervise patient care and further treatment (or ensure that these are supervised by another medical professional); and
- clearly, accurately and transparently record (write down) all administered medicinal products, and the reasons they were prescribed (2).

Similar circumstances are also found in Sweden, France, the Czech Republic, and Hungary. In these countries, off-label prescription of medicinal products is legally regulated, in the overall interest of patients' well-being, and forms part of everyday medical practice. Nonetheless, physicians' choices are not completely unrestricted, as they bear more liability and need to satisfy numerous condi-

Table 1. The premises regarding the off-label use of medicinal products in selected countries.

Country	Off-label practice
Italy	The currently binding law strongly emphasizes the need to obtain prior informed consent from the patient for the off-label use of medicinal products. Article 3 (2) of the Law of 1998 (Legge di Bella) states "in individual cases the physician, under his/her own responsibility, may prescribe an off-label medicine, having provided the patient with sufficient information and obtained his/her informed consent, if there are no other available registered products effective for that treatment, under the condition of existing scientific evidence's confirming the validity of using it (...)". The Italian Drug Agency has developed three lists (including in hematology and pediatrics) with approved indications regarding off-label use.
Australia	According to the Therapeutic Goods Administration, the off-label use of pharmaceuticals does not constitute an infringement (although this has not been the subject of any judicial proceedings). In some cases, a failure to administer a given product, where its non-registered use is supported by reliable data, can actually be treated as professional negligence.
Spain	Royal Decree No. 1015/2009 authorizes physicians to prescribe off-label products in exceptional circumstances if there are no authorized alternative therapies for a particular patient. The Decree states that such off-label use requires obtaining the prior consent from the patient.
Germany	The guidelines issued by the German Federal Joint Committee define off-label use (called "use beyond marketing authorization") as any use "in indications or indication areas" not covered by the authorization, as well as "any use that justifies a variation of the marketing authorization."
Switzerland	The off-label use of pharmaceuticals is regulated by the Health Insurance Law (Article 71a). Physicians are allowed to issue off-label prescriptions (without limitations in oncology) in specific circumstances, i.e. (a) when the use of a given medicinal product is necessary for performing another intervention which is covered by obligatory health insurance, and which has been given a clear priority; or (b) when it can be reasonably expected that the product will bring significant therapeutic benefits in treating medical conditions which are potentially life-threatening, or which can lead to acute or chronic health disorders, and other treatment methods are unavailable.
The Netherlands	The Medicines Act (GW, 2007) defines the criteria under which an off-label prescription can be issued. In compliance with Article 68 of GW, this is only permitted on the basis of protocols and standards developed by experts. If the protocols and standards are still under development, a consultation between the physician and the pharmacist is necessary (regarding innovative drugs). Treating physicians must also inform their patients that a given drug has no registered indications and obtain their consent. They must also be convinced that off-label treatment is scientifically justified.
Malta	Off-label use is not subject to any regulations. Whereas hospitals are generally allowed to use pharmaceuticals for purposes other than indicated, some of them have introduced internal policies obliging physicians to fill in special forms.
Finland	Prescribing off-label products is not legally restricted. There are no national guidelines to that effect, nor is it necessary to obtain any specific licenses for such use.

Source: Matusiewicz W. The use of medicinal products in oncology and hematology regarding indications for use and dosage or administration methods different than those defined in the Summary of Product Characteristics, The Agency for Health Technology Assessment and Tariff System 2012

Table 2. Statistics regarding the use of medicinal products outside registered indications in selected countries.

Country	Off-label practice
Canada	It is estimated that off-label prescriptions account for around 40% of all prescriptions for adults and 90% for children.
Germany	In oncological treatment, off-label pharmaceuticals are administered in 70-80% of cases. It is estimated that off-label use involves 56% of pediatric drugs.
Japan	30% of anti-cancer drugs and 40% of supplementary treatment products are administered off-label.
Austria	50% of drugs in pediatrics and 90% in neonatology are prescribed off-label.
Switzerland	As many as 79% of medicinal products in children can be used off-label.
The Netherlands	In outpatient care, 22.7% of children receive off-label treatment.
USA	One in five prescriptions in the USA is issued off-label.

Source: Matuszewicz W. The use of medicinal products in oncology and hematology regarding indications for use and dosage or administration methods different than those defined in the Summary of Product Characteristics, The Agency for Health Technology Assessment and Tariff System. 2012

tions regarding off-label use. These include the obligation to inform the patient that a given medicinal product will be administered off-label, to conduct prior consultations with another expert, and to receive a positive opinion on the off-label use of the pharmaceutical in question. Although the practice of off-label-use has developed under a variety of country-specific circumstances, it is a common and permitted practice, albeit one that must satisfy certain stipulations (Table 1).

In cancer treatments, the practice of prescribing medicinal products outside their registered indications is widespread. For instance, in Germany, off-label pharmaceuticals are administered in 70-80% of cases (2). When looking at such countries as Canada, Germany and Switzerland, the conclusion can be drawn that the same practice has become common and large scale, and is included in the treatment of pediatric patients (Table 2).

When discussing the use of medicinal products in various countries, the wording of Article 35 of the Declaration of Helsinki is worth remembering; it reads: "In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded, and, where appropriate, made publicly available? (3). It follows, therefore, that anything which is consistent with medical

principles should be considered compliant with the law. Such a viewpoint has also been expressed in the judicial decisions of Polish courts. A decision of the Court of Appeal in Poznań of 26 November 2009 may be considered an example: The Court found that a physician acting in compliance with medical principles, and aiming at the patient's recovery, was adjudged to have been abiding by the law, and should not fear liability. Only those medical procedures that go beyond the principles of medical knowledge and ethics are considered unlawful (4).

Even though Polish legislation does not contain any specific legal definition, the right to use medicinal products off-label can be derived, *inter alia*, from the Act on the Profession of Physician and Dentist of 2018 (5). Article 4 of the said Act identifies the basic principles for physicians: to follow professional guidelines and ethical codes, and to use all available methods with due diligence (5). This provision should be treated by physicians as an indication of how they should act. On the one hand, it refers to the basic directives necessary for undertaking professional activities, and, on the other, it determines certain limits and duties arising from them. The afore-quoted Article contains the phrase "by complying with the guidelines of current medical knowledge" which can be construed as "by following the conclusions drawn from the current medical knowledge" (5). By adopting a specific procedure in a given case, which is justified in the light of medical knowledge, a physician can be understood to have complied with the guidelines of the current medical knowledge. However, the applicable legal regulations do not explicitly define the criteria with which physicians should guide their decision-making. Undoubtedly, such criteria must have a scientific

ic nature, and be developed in accordance with the principles of a recognized, reliable and transparent methodology. It follows then, that it is the physician who makes the decision and determines the sources of knowledge that he/she wishes to apply (6). Presumably, these sources ought to include recognized guidelines, operational standards, recommendations of scientific associations, thematic publications, scientific papers, clinical trials, recommendations and opinions issued by the Agency for Health Technology Assessment and Tariff System, and Summaries of Product Characteristics (6).

The spectrum of off-label use includes guideline-recommended practices (for example, aspirin in diabetes for prophylaxis against cardiovascular diseases), last-resort therapies (for example, tacrolimus for autoimmune diseases, in addition to transplantation), and first-line therapies (gabapentin for painful diabetic neuropathy, in addition to its use in herpes zoster) (7).

The obligation to act with due diligence in the treatment process

“Due diligence” is a key term used in Article 4 of the Act on the Profession of Physician and Dentist. As it has not been exhaustively defined in the binding regulations, it can only be interpreted by referring to both the judicial decisions issued by Polish courts and legal and scientific commentaries on the issue (8). When attempting an interpretation of “due diligence” it is clear that the term at least implies taking those treatment and medical measures in respect of the patient, that appear to be indispensable to both the patient’s state of health and the adequacy and efficacy of the entire treatment process. Among those medical measures, pharmacological treatments have a primary place. In the beginning, when both prognosis and efficacy prospects are at their most promising (the objectives being to achieve a desirable effect, i.e. to improve the state of health, and to inhibit the progression of the disease, or to effect re-emission, or to achieve complete recovery), then pharmacological treatment is appropriate and consistent with the indications of current medical knowledge on therapeutic procedures. This means that the physician is obliged to provide medical services, regardless of the procedure type, by complying with the principles of current medical knowledge and by acting with prudence (8). Therefore, the diagnostic, therapeutic or rehabilitation procedures that are commenced at the moment when they can prove effective in leading to the patient’s recovery, are excellent examples of exercising due diligence. Likewise, medical meas-

ures can be deemed to be appropriate when, for example, in cases of pharmacological treatment, when the benefits outweigh any potentially negative consequences for the patient’s health or life. Due diligence also refers to independent decisions made by physicians in the treatment process that are based on the indications given by current medical knowledge, and that take into consideration specific medical guidelines and recommendations, such as medical standards. Finally, high-quality physician-to-patient communication is also a key element of due diligence.

The duty imposed on physicians to act with due diligence in the treatment process automatically excludes the obligation to achieve a strictly predefined result. This implies that a physician’s task is not only to cure the patient but to take such measures that are likely to lead to an improvement in the patient’s health or their complete recovery. Therefore, the concept of due diligence also entails selecting a suitable therapeutic method that ensures the patient’s safety. This assertion is confirmed in Article 57 (2) of the Polish Code of Medical Ethics, which states: “when choosing specific diagnostic or therapeutic forms, physicians must be driven, in particular, by efficacy and safety criteria, while avoiding patient’s exposure to unjustified costs” (9).

While the above considerations refer to interpretations of what constitutes due diligence in the treatment process, defining its opposite, namely the notion of a “failure to exercise due diligence”, must also be attempted. Polish jurisprudence in this matter was determined in a 1998 decision by the Court of Appeal in Warsaw. The Court ruled that “the diligence expected of a physician must not be viewed as comprising duties which cannot be performed” (10). It can, therefore, be inferred that a physician’s duty is to take any possible measures aimed at curing the patient. However, one cannot expect that the patient will ultimately be cured, as in some cases the physician might not foresee the organism’s reactions to treatment, despite the physician having exercised all due diligence. This view was also stressed by the Court of Appeal in Cracow, which stipulated that “the physician’s fault means a failure to act to the highest standard of diligence which can be exercised with the current methods of treatment applied in a given medical condition, and procedures constituting standard practice” (11). Furthermore, it is also in line with the Supreme Court’s verdict passed on 10 February 2010: “physicians and medical practitioners are obliged to adopt such procedures (treatment) which could guarantee, in observance of the current medical knowledge and due diligence, a foreseeable

treatment effect, in particular without exposing patients to the risk of the deterioration of their state of health" (12). Considering the above, any off-label use of a medicinal product should only proceed on condition that it is in the patient's best interests.

A summary of product characteristics

Polish Pharmaceutical Law contains the following definition: "a medicinal product shall mean any substance or combination of substances presented as able to prevent or treat disease in human beings or animals, or administered with a view to making a medical diagnosis or to restoring, correcting, or modifying physiological functions of an organism through pharmacological, immunological or metabolic action" (13). This definition is not intended to imply that physicians have unlimited leeway when selecting medicinal products, as they "can only prescribe those pharmaceuticals and medical materials which have been allowed for marketing in the Republic of Poland on principles laid down in separate regulations" (5). The use of a medicinal product for therapeutic purposes other than those defined in the marketing-authorization process is considered off-label, i.e. not approved by the authorized registration body. Such refers to cases where a product is not used according to the approved terms that are defined in the product information or patient information that is attached to or included in its packaging (14, 15).

Product information or, more specifically, information on the medicinal product and its use, is regulated by Pharmaceutical Law, which stipulates that issuing an authorization implies approving the medicinal product's Summary of Product Characteristics (SmPC), leaflet, and packaging (13). It should be noted that SmPC's documents are mainly intended for medical professionals, whereas product leaflets are addressed to patients. Item 4.1 of the SmPC contains indications regarding the use of a given medicinal product, and this is similar to the "Directions for Use" section included in the leaflet. Any amendment to an SmPC requires prior approval, and all data included in the document are open-access (13, 16). Every medicinal product available on the market is required to pass a documented risk-benefit profile evaluation. This means that the product's safety has been approved by competent bodies for the indications proposed by the marketing authorization holder and that the product has been tested by the target group of patients in treating a specific medical condition, in accordance with the proposed dosing regimen. Randomized clinical trials are meant to serve the purpose of

determining the efficacy and safety profile of new pharmaceuticals. The costs of such trials are usually covered by the marketing authorization holder. Therefore, their scope tends to be reduced to the absolute minimum, as the entire research process involves a significant financial cost. This assertion is supported by the fact that separate trials must be performed for each indication, dosing regimen, or target group. It is worth noting that conducting the required studies and providing documentation that confirms the safety and efficacy of a registered product, all forms part of the registration documentation, in the absence of which no medicinal product can be legally marketed. Information about the chemical, toxicological, pharmacological, and pharmacokinetic profiles of a medicinal product is found in the product's SmPC. Therefore, the use of a pharmaceutical for purposes other than those defined and included in the SmPC "can make the favorable risk-benefit profile cease to exist" (17).

The primary objective of providing a product SmPC for a given medical treatment is to obtain marketing authorization for the medicinal product. In addition, the SmPC, together with other legally required appendices to the marketing-authorization request, is used as the basis of an assessment report by the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. Finally, the SmPC also forms the basis for the leaflet, which is also appended to the marketing-authorization request.

Several situations are described in the literature where the use of medicinal products beyond strictly registered indications is permitted. These include:

- the use of a medicinal product in a manner, or route, of administration not specified in the SmPC
- the use of a medicinal product in compliance with the registered indications in patients for whom the dosing regimen has not been specified
- the use of a medicinal product for purposes not listed in the SmPC, but for which there are reliable data confirming the product's safety and efficacy
- the use of a medicinal product for a new indication which has not been proven yet, but for which there are scientific grounds for expecting the product's safety and efficacy (18).

Furthermore, medicinal products may be used outside the scope of the registered indications when:

- they are administered in doses outside the intervals indicated in the SmPC, (increased/decreased doses)
- they are administered despite identified contraindications

they have been tested for similar medical conditions but the corresponding SmPC does not cover a given condition (19).

Notably, there is a need to distinguish between two forms of off-label use: in the narrow sense, when a medicinal product is used for purposes other than those registered and listed in the SmPC; and more broadly, when a substantively different kind of off-label use is made that might include changing the dosing regimen, the dosing scheme or the route of administration, or using the product on a certain age group for which no dosing regimen has been determined. Consequently, off-label use in the narrow sense takes place when a medicinal product is administered for purposes other than strictly registered in the SmPC, whereas any other off-label use will be interpreted as falling within a broader perspective.

The physician's responsibility for off-label use

A physician's freedom to prescribe drugs off-label carries important advantages, but also raises the limited matter of legal liability, which can discourage a physician from off-label use, even when there is evidence to support such a use. For instance, there is the interesting case of Diane-35 (cyproterone acetate-ethinyl estradiol). The authorized uses of Diane-35 vary across Europe. Some countries have approved it as a contraceptive for women with hormone-related issues, such as alopecia and excessive growth of facial hair. In others, the drug is authorized only as an acne treatment. In France, the country's medical regulator, Agence Nationale de Sécurité du Médicament et des Produits de Santé, has noted its widespread off-label use for birth control, and there were severe adverse drug reactions (venous thromboembolism) reported (20). In such a case, if there were an adverse drug reaction lawsuit for off-label use, the liability only rests with the physician, and not with the marketing authorization holder, despite the fact that there are differing authorizations and indications across Europe.

In cases where treatment is conducted with a medicinal product whose use for a given purpose has not been envisaged in the SmPC, and there are no other circumstances that would justify its exceptional off-label use, we are dealing with medical experiments. In Poland, this matter is regulated by the Act on the Profession of Physician and Dentist (5). Given the regulations governing the use of medicinal products outside their registered indications, it can only be assumed that a physician resorting to 'experimental' off-label treatment will take identical measures to those conducting a treatment

experiment, with the aim of improving the patient's health and/or achieving a desired therapeutic outcome.

In off-label procedures, it is very important to obtain the informed consent of the patient. This is so because the patient has the right to be an informed participant in their healthcare decisions. Obtaining informed consent is a process by which the healthcare provider treating the patient discloses the appropriate information to a responsible patient so that the patient can make a voluntary choice to either accept or refuse the treatment (22). The physician has the duty to describe, in general terms, why the chosen drug is not licensed for a specific indication or patient population. Physicians must always answer questions from patients comprehensively. It should be noted that the FDA requires explicit written consent for drugs being used experimentally or as a part of research, however, no explicit consent is required for any off-label drug use if it can be argued that, like any other treatment, the drug is being used in the patient's best interests (23). Because of the patient's right to be informed, a consultation must be held. It is suggested that providing patients with information about off-label use can afford health care providers with a greater level of protection from future liability suits (24).

Medical malpractice is a broad term which includes the act of negligence. In fact, 4 elements of tort law dealing with negligence must be proved before liability can be established: 1) the prescribing physician must have an obligation towards the patient, 2) that obligation must be breached, 3) there must be some injury requiring compensation, and 4) there must be a causal link between the breach and that injury. If a patient was harmed by the off-label use of a drug, it must be established during the lawsuit that the prescribing physician had deviated from the required standard of practice.

An analysis of off-label use and practices in the EU

Prevalence among adults

The prevalence of off-label use in EU countries among adults, as compared with pediatric populations, depends on each country's pharmaceutical policy law, regulations and authorization status (25). The main motive for levels of off-label use is associated with the limited number of established clinical indications applied for (26). An obvious and general fact is also that most drugs are registered for, and have been tested in, adult populations between the ages of 18 and 64 years (27) Thus, in most cases, special groups of patients, such as elderly people,

pregnant women, or people suffering from obesity, hepatic and renal dysfunctions, along with a variety of other common conditions which are not fully examined, are excluded (28). In the abovementioned report on 23 studies, including 6 EU member states, and ranging across adult populations, the level of prescription of off-label drugs in hospital settings ranged between 7% and 95% (28). In contrast, a report on 13 studies, also from 6 EU Member states, indicated that the prescription of off-label drugs in outpatient settings ranged between 6% and 72%. These results seem to prove that there is an unmet need for the introduction of international regulations and statements in EU countries which will support drug licensing.

Summary

In Poland, the use of medicinal products outside registered indications, i.e. in a manner different from that indicated in the SmPC, tends to raise serious concerns, especially given the lack of adequate legal regulations. Nonetheless, examples of other countries where off-label use has become both common and legally permissible testify to the need to develop such regulations in Poland. Therapies involving medicinal products administered outside strictly registered indications are most frequently used in oncological diseases. Obviously, they mainly involve adult populations, but pediatric patients are also included. In fact, based on the review of the literature on the subject and the opinions expressed by medical professionals, the use of off-label products among pediatric patients is frequent. As many as 80-90% of pharmaceuticals used in children to effectively treat cancer do not have any registered indications for that type of medical condition (29). Therefore, off-label practice, despite the lack of specific legal regulations, is becoming common. This mainly results from a physician's duty to perform their profession in line with current medical knowledge, to use available methods and preventive measures, and to diagnose and treat medical conditions in compliance with the principles of professional ethics, and with due diligence (5). In view of this provision, a physician, aware of their responsibility for the health and life of the patient, who should be treated with due diligence, adopts the best-possible therapy to cure that patient, in accordance with current medical knowledge, upholds the standards and recommendations developed within medical circles, exercises the utmost prudence, and follows adopted medical practices.

Declarations of interest

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