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*Short communication*

# Role of the pharmacovigilance systems in collecting the information for off-label use of drugs in EU

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## Introduction

Off-label prescribing is part of medical practice and may be necessary to fulfil the need of individual patients, due to the absence of suitable, authorized alternatives. Although EU-legislation does not directly regulate off-label use, off-label use received particular attention in the new EU pharmacovigilance legislation. Directive 2010/84/EU acknowledges that off-label use exists and marketing authorization holders (MAHs) are responsible to provide all available information on their products – including the results of clinical trials or other studies – as well as any use of the product outside the terms of its marketing authorization obtained in postmarketing period through established PV systems. The drivers of off-label use of medicines are multiple and involves many stakeholders, namely regulatory agencies, the industry, physicians, insurers, professional medical associations and consumers with distinct and often conflicting interests. The main problem associated with off-label use is the information deficit about a product's efficacy and the prospect of exposing patients to higher risks, whose adverse health outcomes could remain unknown to public authorities if an implemented pharmacovigilance system itself are malfunctioning or deficient in the necessary oversight mechanisms. Off-label practices could posture a threat to public health as a result of extensive uncontrolled use of drugs out of their marketing authorization. Well established PV systems are important in the process of obtaining of a product to scientifically valid and statistically significant evidence for drugs in confirmation of positive benefit/risk ratio.

This research aims to identify specific provisions regarding engagement of PV systems in surveillance of off-label use implemented in EU countries in an attempt to obtain solid base for regulation in The Republic of North Macedonia.

## Materials and methods

Relevant EU, US and Macedonian legislations have been reviewed, in general, as well as PubMed, Medline and other relevant websites with articles evaluating the impact of EU regulatory requirements and activities related to off-label use of medicines.

## Results and discussion

The preamble to Directive 2010/84/EC states that Member States should operate pharmacovigilance systems to collect information that is useful for the monitoring of medicinal products. This includes information on suspected adverse reactions as a result of the use of a medicinal product, also in case this use was off-label. New pharmacovigilance legislation also stresses the importance of providing patients with possibilities to report suspected adverse drug reaction, including those of off-label use and post authorization studies may be aimed at collecting data to enable the assessment of the safety or efficacy of medicinal products in everyday medical practice.

According to Court of justice in European Union (CJEU) only when doctors could conclude the state of health of a patient demands the administration of a medicinal product for which an authorized equivalent does not exist or is unavailable on the market under consideration is appropriate. Regulation in France support safer off-label utilization, improvement of knowledge regarding the efficacy of off-label uses and encouragement for pharmaceutical companies to file requests for extensions of MAs. Regulation in Italy supports, the obligation of the physicians prescribe a medicinal product,

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they should observe the therapeutic indications, routes and methods of administrate on provided for by the MA issued by NC, updated in 2007 with escalated requirements for off-label use by imposing the need for at least Phase II clinical studies. In Germany, judicial decisions have led to changes in the legal treatment of off-label drugs. For the reimbursement approval three criteria should be met, a severe illness that has a lasting negative impact on an individual's quality of life, no conventional treatment option and off-label use of the medicine has a reasonable prognosis of success. A main argument for not having specific measures in place is that off-label use is the responsibility of the prescriber; the prescriber is autonomous to prescribe.

The systematic literature review shows that off-label use in children exists in EU Member States and 33% of the total number of the prescriptions investigated in that particular study population was an off-label prescription. Off-label use may be due to the fact that medicines are usually registered for a limited number of indications, and not fully studied in specific patient groups (pregnant women, elderly or people with specific comorbidities, like renal and hepatic failure). The literature review from 23 studies including data from six EU MS presented that off-label use in adults frequently occurs in the hospital setting: a range in prevalence of 7% to 95% of all prescriptions was found. Studies with a high prevalence of off-label use covered a range of therapeutic areas (oncology, autoimmune diseases, and palliative care) and use during pregnancy. Most studies reported in literature on off-label use in adults focus on specific therapeutic areas, such as oncology, psychiatry, or on expensive medicinal products, such as intravenous human immunoglobulins and TNF-antagonists (used in rheumatology). Several representatives stated to have no specific information on the extent of off-label use in rare diseases. The obtained results have confirmed that regardless of a common feature existing in many jurisdictions when it comes to medical practice not being subject to the regulation of medicines, an extensive off-label use would still weaken the public expectation that there has been a proper evaluation of a product's safety and efficacy. Such harm may result from an off-label medicine prescribed by physicians who relied on journal articles that sometimes do not provide adequate, neutral studies, because partial stakeholders with strong economic interests. Off-label use would represent a threat to a patient's safety in particular due to serious adverse events resulting from a medication use different from the treatment for which the medicine has been approved as 73% of off-label prescriptions in the EU lack evidence of clinical efficacy. Another negative aspect associated with off-label use is the increase in healthcare costs.

But according to the literature results point out that, there are many advantages related to the off-label use of medicines. If there is strong evidence indicating that the benefits of a determined off-label use outweigh the risks, then decreasing to treat the condition pretenses greater danger for the patients. Off-label use may represent the single possible treatment available for patients who cannot rely on authorized medicines, but also signify a path to innovation through which additional indications extension for an authorized medicine are discovered. The regulatory approval process may often lag behind scientific advancements and the presence of high-quality evidence, which is why an adequate control of off-label use could induce the desired repurposing of drugs, and the main tool in that process are well established PV systems. In that line off-label use enables innovation in clinical practice as physicians could look for more suitable creative solutions for their patients, who may thereby gain earlier access to medications, especially when other drugs are with suboptimal efficacy. Many regulatory agencies operate in legal systems that separate regulation of medicines from doctors' freedom to prescribe. Some EU countries, France, Italy and Germany, have adopted regulatory frameworks that allow the reimbursement of medicines for off-label uses, which encourage such prescriptions by physicians, regardless of approved alternatives available in the market.

The importance of well-established PV practices were confirmed during COVI-19 pandemic when the many drugs, tocilizumab, chloroquine, azithromycin, ivermectin and favipiravir as well as high doses of vitamins.

## Conclusion

The performed evaluation and comparison of the EU and North Macedonian legislation have confirmed that the off-label use of drugs in our country is not regulated. It is inevitable to adopt and implement the positive experiences form EU countries in our regulation and engage the PV system in order to obtain valuable data trough appropriate surveillance of off-label use of drugs and employment of the good pharmacovigilance practices in terms of collection and follow-up of cases of off-label use (including cases not associated with suspected adverse reactions) as well as in terms of additional structured investigations (drug utilization studies, searches in databases).

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