



Declaration on Good Off-Label Use Practice

The use of medicines off-label is often a necessity in areas of unmet medical need. As recently shown by a study commissioned by the European Commission on the off-label use of medicinal products in the European Union (EU), the prevalence of off-label use in the EU in both the paediatric and adult population is high in a broad range of therapeutic areas (especially oncology, psychiatry, neurology and rheumatology) in both hospitals and outpatient settings.¹

Off-label practice poses a range of quite different challenges. First, the use of an off-label product implies a number of ethical and legal issues for healthcare professionals. Their choice to prescribe and dispense an off-label product should be based solely on therapeutic considerations in the best interest of the patient and ideally supported by evidence-based guidelines. Second, just as with any unlicensed medicinal product, the off-label use of medicine potentially carries an increased risk for patients. While off-label prescribing may be necessary and justified for medical reasons, an adequate level of evidence in terms of efficacy and safety is necessary. Third, in off-label prescribing and dispensing, patient information and consent is especially important. This aims to ensure that the patient is aware of the benefits and risks of off-label use and that both good and bad outcomes are duly reported.

While not optimal, off-label prescribing may remain essential to address unmet medical needs of patients. However, the manner in which countries deal with the off-label use of medicines is not harmonised across the EU.² In this context, some EU Member States have passed legislation that promotes the off-label use of medicines for economic purposes. These developments endanger agreed European scientific standards, thus putting patients' safety at risk. We thus highlight the importance of preserving the European regulatory framework to ensure the safety of patients, while ensuring good off-label use of medicines for patients in need.

Therefore, it is necessary to summarise the principles of Good Off-Label Use Practice (GOLUP) to guide practice as it currently exists in different Member States of the EU. The following GOLUP principles stem from decades of research and clinical practice and serve to create a framework to ensure that the interests of patients, prescribers, pharmacists and the public at large are protected. The signatories of this declaration call on the European Medicines Agency and other national regulatory bodies to adopt strict guidelines to support healthcare practitioners in ensuring safe drug therapy when licensed medicines do not meet the needs of the individual patient, while making sure that public health remains a priority and is not undermined by economic interests.

¹ Study on off-label use of medicinal products in the European Union, NIVEL, Dutch National Institute for Public Health and the Environment, and the European Public Health Alliance, published on 28 February 2017.

² Ibidem.



Off-label use of medicinal products should only occur if all the following criteria are met:

- 1. Presence of a medical therapeutic need based on a current examination of the patient by a suitably qualified health care professional;**
- 2. Absence of authorised treatment and licensed alternatives tolerated by the patient or repeated treatment failure;**
- 3. A documented review and critical appraisal of available scientific evidence favours off-label use to respond to the unmet medical need of the individual patient**
- 4. Patients (or their legal representative) must be given sufficient information about the medicines that are prescribed to allow them to make an informed decision;**
- 5. Presence of established reporting routes for outcomes and adverse events linked to off-label use.**

In all instances, off-label prescription should only occur after a suitably qualified health care professional has conducted a thorough assessment of the needs of the individual patient. Suitably qualified health care professionals have the freedom to uphold their pledge to act ethically towards patients, according to scientific evidence and put the patient's interest first when prescribing off-label medicines. They should be supported by the public bodies and authorities responsible for the approval and usage of medicines, whose role is to protect public health, notably with the adoption of clear guidelines at EU-level.

Background

Before reaching the market, medicines need to obtain a marketing authorisation for a specific indication based on the balance of the desired effects or 'benefits' of the medicine against its undesired effects or 'risks'. The information regarding how, and by whom, the medicine

should be taken, based on extensive testing of the product's quality, efficacy and safety, is described within its label (packaged insert). This strict procedure is designed to maintain the highest levels of patient safety and minimise adverse events.

EU law does not define the term "off-label use," since it presumes that all medicines are used only for their given indications and in the manner for which the marketing authorisation has been obtained. However, the term "off-label" is used in EU legislation on veterinary medicines (Directive 2001/82/EC) and it is possible to apply the definition by analogy to all medicines. Moreover, Article 5 of Directive 2001/83/EC contains certain exceptions from the marketing authorisation requirement when required to fulfill a special medical need of the patient, as carefully assessed by the suitably qualified health care professional himself on a case-by-case basis. These elements clarify that prescribing of products that are not authorised, or not authorised for the indication in question, is a possible exception to the general rule but must be motivated solely on the proven medical interest of the patient.

Off-label use can therefore be defined as the practice of using a medicine outside of its authorised indication, dose, route of administration or patient group. It plays an important part in medical practice since it may be of benefit to patients when no other authorised treatment option is available. Most commonly, it involves the use of medicines well characterised for their primary indication.

Recently, we have also witnessed a growing trend of promoting the prescription of off-label medicines without a medical rationale, but with other motives, such as cost-containment and economic reasons being employed. EU Member States are passing legislation / guidelines / or establishing practices promoting off-label use mainly to reduce healthcare spending. This has been the case in Italy, France and Denmark. These practices create unnecessary and avoidable risks for patients, often without their consent, and lower scientific standards set out by EU legislation. This view is supported by the European Court of Justice, which has ruled that patient safety must always prevail against any economic rationale.³

³ Judgment of Court of Justice of the European Union of 29 March 2012, European Commission v Republic of Poland, Case C-185/10.



A major challenge in the area of off-label use is related to the fact that there are limited incentives for the pharmaceutical industry to extend the labelling of existing medicinal products. Companies struggle to establish safety and efficacy in closely related conditions or in the same condition as, for example, pregnant women, the elderly or children. While recognising this is an important issue, the Declaration does not look specifically at this complex issue, but rather tries to put forward the basis for a harmonised approach on when and how off-label prescription should take place across Europe.⁴

Good Off-label Use Practices – A closer look

1. Presence of a medical therapeutic need based on a current examination of the patient by a suitably qualified health care professional

Signatories agree that off-label treatments should be initiated by a suitably qualified health care professional in collaboration with the patient (or legal representative) based on a medical assessment of the therapeutic need. Studies suggest that the use of an off-label medicinal product contains a higher risk of adverse events. In addition therapeutic benefit has not been established irrefutably for the particular patient group or indication for which it is being used. This added risk of off-label drug use is only justifiable if there is a clear medical need that cannot be fulfilled with available licensed drugs or formulations and that, considering the available evidence, the reasonable chances of efficacy outdo the likely risks to the patient. This is especially the case for:

- Drugs licensed for use in adults, but not in children of various age groups. Not treating children with these drugs would limit treatment options and jeopardise outcomes;
- Drugs used during pregnancy and breastfeeding;
- Drugs used to treat orphan conditions which lack licensed medicines.

2. Absence of authorised treatment and licensed alternatives tolerated by the patient or re-peated treatment failure

Many diseases continue to lack any licensed medicinal product. This is often the case for rare diseases and diseases found in childhood or pregnancy. In these cases, or when the licensed standard treatment has failed or is not available in a particular country, suitably qualified health care professionals may decide to prescribe an off-label product as long as they receive patient/carer consent and there is acceptable evidence to support the suitably qualified health care professional's decision. However, this condition should not result in Member States delaying entry into market of a particular product so they can justify the use of an off-label alternative for economic reasons.

3. A documented review and critical appraisal of available scientific evidence favours off-label use to respond to the unmet medical need of the individual patient

Even when authorised treatments have failed or there are no other on-label treatments available, medicines should only be used off-label if there is scientific evidence in the literature of their potential benefit for a particular condition. Ideally, published reports of well-designed clinical studies will be available or support for the off-label use will be provided in peer-reviewed literature. Where possible, the suitably qualified health care professional's decision should be informed by evidence-based consensus guidelines.

While it may not always be possible to gather this level of evidence, especially when the patient is a child or a pregnant woman, there needs to be an overall positive therapeutic assessment as reflected by clinical evidence, expert opinion, best practices, and/or authoritative guidelines. In addition, there should be an absence of potential clinically important concerns about the treatment option, such as increased toxicity with no substantial therapeutic gain as compared to the authorised standards of care.

⁴ Study on off-label use of medicinal products in the European Union, NIVEL, Dutch National Institute for Public Health and the Environment, and the European Public Health Alliance, published on 28 February 2017.



4. Patients (or their legal representative) must be given sufficient information about the medicines that are prescribed to allow them to make an informed decision;

The patient or his/her legal representative should be informed of the possible risks and benefits of the medicines that are prescribed to allow them to make an informed decision on the suggested treatment.

Educating the patient and having their consent is an important element of good off-label use practices for a number of reasons. First of all, given uncertain risks of adverse reactions sometimes involved with the use of an off-label product, it is important that the patient understands the proposed treatment option and is informed of the knowns and unknowns. Secondly, patients should be made aware of the product they are being prescribed and how they can accurately self-report adverse events. This is crucial as the off-label use of medicines creates uncertainty around liability and suitably qualified health care professionals may be less likely to report adverse events experienced by the patient. Thirdly, since off-label use of drugs is not addressed by the patient information leaflet of the product, no guidance or reference is available to patients with regard to information on adverse effects, precautionary measures and dosing information. Therefore, it is important to specifically inform patients about these aspects.

Some medicines are routinely used outside the terms of their licence, for example in treating children. In emergencies or where there is no realistic alternative treatment and such information is likely to cause distress, it may not be practical or necessary to draw attention to the licence.

5. Presence of established reporting routes for outcomes and adverse events linked to off-label use

The results of the off-label use must be reported in the patient file, whatever the outcome, and scientific publications on outcomes of off-label drug use should be encouraged. Pharmacovigilance activities may be hindered by the off-label use of products because of inaccurate reporting of adverse events and the fact that patients may not always know they are being prescribed off-label. Patients should thus be encouraged to report therapeutic ineffectiveness and/or adverse effects to their prescribing suitably qualified health care professional or report the adverse effect directly to a national pharmacovigilance agency if reporting routes for patients are available.

If available and accessible to patient reporting, the EudraVigilance platform (the European data processing network and management system for reporting and evaluating suspected adverse reactions) could be used to gather better data on adverse effects. However, patients still lack all the necessary information about self-reporting as they may not always read the product's label.

Equally important is the sharing of knowledge about clinical outcomes. In the academic literature there is a tendency to report only positive experiences with off-label products rather than recording negative outcomes. This introduces a bias that is difficult to correct. However, it is also true that routinely collected data may be difficult to publish without formal prospective ethical review. A solution to this problem is to create explicit research registries to chart patient outcomes after specific off label treatments. Greater use of patient registries should be strongly encouraged.⁵

⁵ Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight, *The Lancet Psychiatry* Volume 4, No. 5, p419–426, May 2017.



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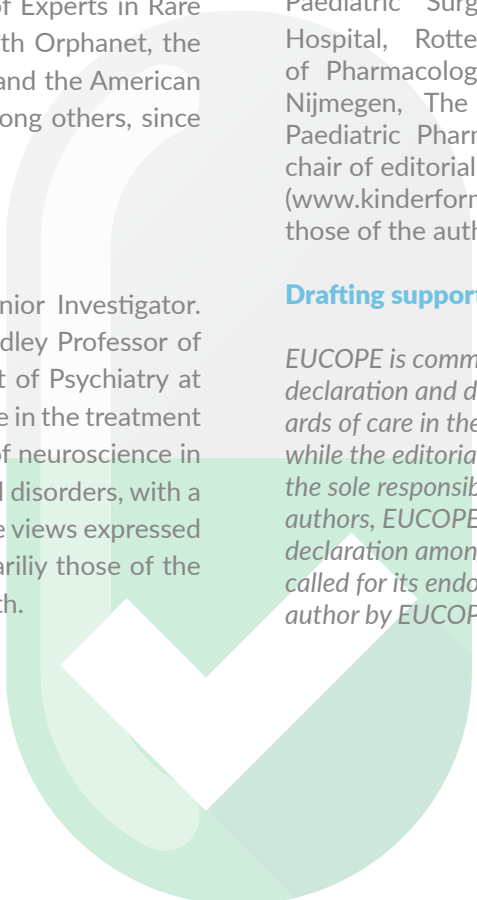
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