

REGULATING OFF-LABEL USE OF **MEDICINES IN EUROPE**



WHAT IS OFF-LABEL USE?

Off-label refers to the use of an authorised pharmaceutical product outside the terms of its marketing authorisation; therefore, not in accordance with the information in the Summary of Product Characteristics. Off-label occurs when a medicine is used for a therapeutic indication other than that approved by a regulatory authority, or in a different dosage, frequency, method of administration, or used in a group of patients for which it has not been authorised.

Off-label use happens in all patient groups, but it is more common among certain patient populations. According to the '[Study on off-label use of medicinal products in the European Union](#)', such uses are particularly widespread in paediatrics—where children are often excluded from clinical trials—and in the area of rare diseases. Pregnant women and the elderly are also groups of concern.

Oncology, hematology, psychiatry and rheumatology are frequently mentioned in the literature as clinical areas in which off-label use occurs.¹

Off-label uses have not undergone the type of benefit-harm assessment required in the procedure for medicines' marketing authorisation. Yet, doctors might consider prescribing a medicine outside its approved label when there is no available treatment for the patient (or if an available treatment has not been effective). Off-label prescription is part of medical practice and may be informed by reliable scientific evidence. However, it has been reported that healthcare professionals regularly prescribe medicines off-label with levels of evidence considered to be low.^{2,3,4} This is particularly problematic because off-label use lacking strong scientific evidence is associated with higher rates of adverse events.⁵

While the promotion by pharmaceutical companies of off-label uses is illegal, it does happen.⁶ The commercial interests at stake, the lack of standard regulatory review, and uncertainties about liability and patients' rights are all factors that mean off-label use should be approached with caution.

HOW IS OFF-LABEL USE REGULATED IN EUROPE?

In 1965, in the aftermath of the thalidomide (Contergan®) catastrophe, the European Union (EU) adopted the pharmaceutical Directive 65/65/EEC, which requires all medicinal products to obtain a marketing authorisation by regulatory authorities before they can be made available. To obtain an authorisation, pharmaceutical companies must prove that the medicine meets quality, safety and efficacy standards.

Today, the EU pharmaceutical marketing authorisation framework is primarily regulated through Directive 2001/83/EC and Regulation (EC) 76/2004. The EU legislation includes some exceptions to the requirement of marketing authorisation (e.g., compassionate use⁷ and medicinal products supplied "in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility").⁸ EU legislation does not, however, regulate the practice of medicine (nor prescription practices at the individual level, either on-label or off-label).⁹ Nonetheless, some EU pharmacovigilance requirements extend to off-label uses. For example, Member States and marketing authorisation holders are required to collect/report information on suspected adverse reactions arising from the use of medicines outside the terms of the marketing authorisation. Some specific provisions about off-label use might be found in a Member State's domestic laws. For example, in Spain the Royal Decree 1015/2009 establishes that the prescription of medicines off-label must be exceptional, limited to situations where there is no authorised alternative for the patient and subject to his/her consent.¹⁰

The Decree imposes some obligations on healthcare professionals (e.g., justify the off-label use in the patient's clinical history, report any suspected adverse drug reactions (ADR) and follow any issued prescription/dispensing restrictions as well as the therapeutic protocol of the medical centre). For their part, marketing authorisation holders have to report suspected ADRs to the authorities and give notice of any information that could have an impact on issued recommendations of use. The Spanish medicines agency can issue recommendations on the off-label use of a medicine when the risk to patients can be reasonably foreseen, in the case of medicines subject to restricted prescription, or when the use of the drug in these circumstances has relevant healthcare impact.

In France, similar provisions exist through the 'Recommendations Temporaires d'Utilisation' (RTU). RTUs can be issued by the French medicines agency when there is an unmet therapeutic need and where, based on available evidence, it is assumed that there is a favourable benefit-harm balance for off-label use.¹¹ The RTUs, which can last up to three years, impose the obligation on the marketing authorisation holder to collect data on therapeutic benefit, adverse effects and on the real conditions of product use. The RTU framework was established by law and its objectives are twofold: Firstly, to make the use of medicines prescribed off-label safer while improving knowledge about the benefit-harm balance of such use. Secondly, to encourage pharmaceutical companies to apply for marketing authorisation extension (move from 'off-label' to 'on-label').

German law also includes some specific provisions on off-label use in the regulation on health insurance (§35c SGB V). Formally, the G-BA (Federal Joint Committee) regulates the access to off-label use.¹² Accordingly, the prescription of medicines for specific non-authorised uses is permitted if the German Drug Regulatory Agency's Off-Label Commission issues a positive opinion based on the assessment of available evidence. Furthermore, the consent of the pharmaceutical company concerned to the new use is required.

Healthcare professionals must abide by the decisions. So far, 26 positive opinions have been issued, a further 14 were negative.¹³

Not all Member States have specific regulations on off-label use,¹⁴ but this does not mean that off-label prescription is illegal. In fact, it is common understanding that it is up to healthcare professionals to judge which are the best treatment options for the patient, and some recommendations on off-label uses can be found in medical guidelines. With regard to reimbursement, it will be more or less likely that off-label uses are covered, depending on the country in question.

The '[Study on off-label of medicinal products in the EU](#)' provides a good overview of the way in which Member States deal with off-label use.

THE WAY FORWARD?

The use of medicines outside the approved label is common, and the drivers behind these uses are diverse, as are their consequences. On one hand, off-label use undermines the medicines marketing authorisation system and raises concerns about patient safety, particularly when decisions are based on poor scientific evidence.

At the same time, there are situations in which off-label use is justified from a medical point of view.

Because of the implications of off-label use at patient level, healthcare professional level (e.g., liability issues), and to public health budgets, it is important that such uses are regulated. Member States should adopt some key principles that guide off-label prescription, adopt measures aimed at enhancing the collection of information and scientific evidence on off-label uses and issue recommendations for use where needed.

In addition, concrete initiatives are required to facilitate drug repurposing so off-label uses that are supported by strong safety and efficacy data obtain marketing authorisation. Some proposals on regulatory action are presented here for consideration.

1. A REGULATED APPROACH TO THE OFF-LABEL USE OF MEDICINES

Guided by the need to protect public health, Member States' pharmaceutical laws should adopt some key principles that guide the off-label prescription of medicines. Taking into account the concerns inherent in the use of medicines under conditions other than those approved by regulatory authorities, such uses should be exceptional in character (unmet medical need), driven first and foremost by the need to ensure best patient care, and respect the principle of informed consent by the patient. Competent authorities should take an active role and issue specific recommendations for use (e.g., when off-label use is common in a certain patient population and/or when there are safety concerns). Healthcare professionals and medical centres should be required to take into account such recommendations.

Continued collaborative efforts among Member States are needed to increase understanding of the extent of off-label use, and identify disease areas and patient groups where such uses are common. Member States should exchange information—and learn from each other—about ways to regulate the off-label use of medicines. The European Commission and regulatory networks, including the Heads of Medicines Agencies, have an important role to play by promoting and enabling these discussions among Member States.*

2. PROMOTE THE COLLECTION OF DATA FOR DRUG MONITORING AND PROTECT PATIENTS

The Declaration of Helsinki states that the use of unproven interventions "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."¹⁵ In order to protect patients and improve knowledge about medicines used in conditions other than those authorised, it is crucial that off-label uses are closely observed, suspected ADRs are reported in a timely fashion, and safety signals are identified and monitored.

*In foras such as the Commission's Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP") and the HMA's Working Group on Timely Access.

Competent authorities should take all necessary measures to optimise the collection of data on off-label uses for drug monitoring purposes. The use of patient registries should be promoted and marketing authorisation holders should be required to set them up, where needed. The use of medicines off-label in vulnerable groups, such as children are situations of special interest. Registries must be well-designed to minimise bias, and could ultimately complement data from randomised controlled trials (RCTs), which are the most suitable studies for drug benefit assessments.¹⁶ Collected data must be publicly available while respecting patient privacy. Through its various funding streams (e.g., the Health Programme), the EU should continue supporting projects aimed at exchanging best practice on patient registries, improving quality and facilitating interoperability.*

It is also crucial to promote and facilitate direct patient reporting of ADR. Concrete action points Member States should engage in are:

1. Implement awareness raising campaigns with the help of patient and consumer organisations.
2. Set up effective and user friendly mechanisms to report ADRs directly to competent authorities (e.g., enable online reporting, including through mobile apps).**
3. Make ADR reporting processes more inclusive by keeping patients informed of the outcomes of evaluations and sharing alerts.¹⁷

Greater efforts are needed to increase ADR reporting among healthcare professionals, and off-label use is an area of particular interest.

Regardless of whether a medicine is being used on- or off-label, Member States should set up compensation funds for victims of ADR, without prejudice from any obligation that should be borne by the marketing authorisation holder.

Failure by companies to give notification of suspected ADRs to competent authorities on time, the promotion of medicines for off-label use, or the provision of misleading information on approved indications, are circumstances that must be taken into account when considering liability.

3. CLOSE MONITORING OF PHARMACEUTICAL PROMOTION AND INCREASED AWARENESS AMONG HEALTHCARE PROFESSIONALS

Healthcare professionals are often exposed to promotional activities from the pharmaceutical industry, which seeks to increase product awareness and drug prescriptions. When companies promote medicines at the expense of safer or most cost-effective treatment options, there is a risk of compromising patient care and public health budgets. A well-known example of the marketing of harmful off-label use is GlaxoSmithKline's promotion of antidepressant paroxetine (Paxil®) in children and adolescents.¹⁸ Although promotion for off-label uses is illegal, companies partake in such practices.¹⁹ ²⁰ A key problem is that governments often 'delegate' drug promotion responsibility to industry associations, although industry self-regulation carries an inherent conflict of interest. In fact, findings on the prevalence and severity of the breaches to the industry codes that regulate drug promotion show a "discrepancy between the ethical standard codified in industry Codes of Conduct and the actual conduct of the industry."²¹ It is therefore crucial that governments take full responsibility for supervising pharmaceutical promotion and apply dissuasive economic sanctions when companies breach the law, and oblige manufacturers to publicly rectify misleading claims.

At the same time, more awareness among healthcare professionals on the implications of pharmaceutical promotion to clinical practice is needed. Despite its importance, the issue of pharmaceutical promotion is barely addressed in medical training.²²

**For example, initiatives such as the PAtient REgistries iNiTiative (PARENT) <http://www.patientregistries.eu/general-info>

*** EU funded [WEB-RADR](#) project has developed mobile apps for patients and healthcare professionals to report suspected ADRs to national competent authorities, and receive up-to-date information and news alerts. The United Kingdom, the Netherlands and Croatia have participated in the project. The region of Toulouse in France also offers this [reporting option](#) to patients. These type of initiatives should be expanded.

Medical students have made interesting proposals for structuring education on pharmaceutical promotion and conflicts of interest in the medical curriculum, which would instigate critical thinking (see the [American Medical Student Association's PharmFree](#) curriculum model). In France, the demands from medical students groups to better regulate interactions with the pharmaceutical industry were captured in an ethical and deontological charter adopted in 2017 by deans of medical faculties.²³ Similar initiatives should be followed in other countries. Likewise, more public funding should be allocated to support independent continuing medical education to strengthen healthcare professionals' skills on evidence-based medicine (e.g., critical assessment of information on medicines).

4. PUBLIC FUNDING FOR INDEPENDENT CLINICAL TRIALS

Decisions on medicines use should always be based on robust scientific evidence on benefits and harms. Well-designed RCTs are the most suitable studies for drug benefit assessments. When intellectual property (IP) rights over a medicine expire and companies have exhausted all opportunities to extend them, originator companies have little interest in investing in clinical trials to explore other uses. The use of drugs off-label might discourage additional research since companies are already making revenue from an expanded use of the medicine. Public funding for biomedical research and development (R&D) is particularly relevant in those areas where there is little commercial interest. Publicly funded clinical trials can fill in current gaps and help improve knowledge about the benefit-harm balance of medicines in non-authorised uses. But greater commitment is needed at all levels to boost independent research.

Research funding programmes, including the EU's Framework Programme (which has an overall budget of €80 billion for 2014–2020 with prospects of increasing in the future), should prioritise research in areas of societal challenges and allocate substantial resources to support clinical trials conducted by non-profit organisations and other non-industry

stakeholders. Publicly-funded R&D in the area of pharmaceuticals should always be driven by health needs and guided by principles of open data and open access (including timely publication of clinical trial results in publicly available registries), therapeutic advance, and medicines affordability to ensure public return on public investment.²⁴

In addition, the EU and Member States should map out innovative initiatives aimed at encouraging and supporting independent research on medicines and learn from best practices. An interesting initiative for consideration is the programme launched in 2005 by the Italian Medicines agency (AIFA) to support independent research on medicines in three main areas: Rare diseases and drugs for non-responders, head-to-head trials, and strategies to improve the appropriateness of drug use and pharmaco-epidemiology studies.²⁵ The programme was financed through an hoc fund set up by AIFA, to which pharmaceutical companies had to contribute 5 percent of their annual expenditure allocated to promotional initiatives aimed at physicians. In the first three years of the programme, alone, €45 million was made available per year, 50 percent of which supported projects on independent research and drug information. The majority of funded projects were clinical studies (75 percent).²⁶ Another interesting initiative is the Trial Programme from the Belgian Health Care Knowledge Centre (KCE), which supports research by non-commercial entities. The programme focuses on comparative effectiveness trials and aims at improving patient care and the efficient use of healthcare resources and budget.²⁷ The Netherlands and the United Kingdom are also countries with interesting initiatives in this area. Public funding of clinical research and clinical trials is particularly relevant because it has been found to be a good investment of public money, or can have a significant impact on clinical practice.²⁸

In addition to funding clinical trials, the EU and governments need to fund programmes that help enhance the capacity of non-profit organisations to conduct R&D.

Support to initiatives, such as the European Clinical Research Infrastructure Network (ECRIN), which provide assistance to academics and independent researchers to overcome barriers in the conduct of multicentre and international clinical trials, must be continued and expanded. Governments can also help promote clinical research by academic groups by supporting the establishment of centres of excellence.²⁹

5. DRUG REPURPOSING: GOING FROM 'OFF-' TO 'ON-LABEL'

Although governments can adopt measures to strengthen the protection of patients who take medicines off-label and promote the collection of safety and efficacy data on such uses, off-label ultimately remains a grey area with implications at different levels. When there is robust evidence supporting the use of the medicine outside the approved label, such use should become on-label. 'Drug repurposing' involves the process of identifying a new use for an existing medicine outside the scope of the original label, and registering it. Research on new uses of off-patent medicines is often led by academic or other non-profit institutions. A key challenge is to bridge the gap between research conducted by non-commercial actors on new drug uses and the extension of the marketing authorisation for these medicines. Some interesting proposals have already been formulated in the context of off-patent medicines or near-to-patent expiry. An example of this is allowing non-commercial entities to flag the need for a medicines marketing authorisation extension based on the positive results of independent clinical trials (see [this paper](#) from the Anticancer Fund). The idea is that where the regulatory agency would issue a positive opinion based on the data submitted, it could encourage pharmaceutical companies to initiate a marketing authorisation extension procedure relying on the evaluation report of the data already submitted.

Regulatory agencies can also play a proactive role and invite companies to trigger marketing authorisation extension procedures. For example, when data is collected as part of pharmacovigilance requirements or recommendation of use (e.g., French RTU system), it could be suggested that the off-label use is of therapeutic benefit and therefore a potential candidate for extension. Companies could also use the results of independent clinical trials in marketing authorisation extensions, which they initiate. All these three options are complementary and non-mutually exclusive. Regardless of the route, the processes to register off-label uses must be subject to the same evidentiary requirements required in marketing authorisation processes.

Certainly, there are no straightforward solutions on how to authorise new medicines uses where there is little interest from marketing authorisation holders to do so. This is particularly the case in medicines that are off-patent.

Nonetheless, it is increasingly acknowledged that it is necessary to address current gaps. Drug repurposing must be further debated in order to find practical solutions, and commitment from all parties concerned is required. Closer dialogue between regulators and academia/research institutes is needed to explore the engagement of these stakeholders in regulatory processes.

In proposing solutions, it is important to consider the ultimate goal: To ensure affordable access to medicines that meet patient needs. Taking into account the increasing challenge of high-priced medicines and concerns with current IP rules, it would be a grave mistake to rely on expanded IP rights as a solution to encourage drug repurposing. Instead, the best way forward is to support independent research, strengthen the role of regulatory agencies, and ensure generic competition.

CONCLUSIONS

Off-label uses of medicines have not undergone the type of benefit-harm assessment required in the procedure for medicines marketing authorisation. Yet, off-label use is common, particularly among certain patient groups. The drivers behind these uses are as diverse as the consequences. On one hand, off-label use undermines the medicines marketing authorisation system and raises concerns on patient safety, especially when decisions are based on poor scientific evidence. But there are situations in which off-label use is justified. Because of the implications of off-label use at the patient level, healthcare professional level (e.g., liability issues), and to public health budgets, it is important that:

1. Off-label use is regulated and driven by the need to protect people's health.
2. Data collection processes for drug monitoring are strengthened.
3. Competent authorities take full responsibility for the supervision of pharmaceutical promotion on off-label uses, perform active monitoring, and apply dissuasive sanctions.
4. The allocation of public funding for independent clinical trials is prioritised.
5. Measures to facilitate the registration of off-label uses with a positive benefit-harm balance are adopted.

REFERENCES

1. Weda M, Hoebert J, Vervloet M et al (2017). *Study on off-label use of medicinal products in the European Union*. NIVEL, EPHA, RIVM, Utrecht.
2. Radley DC, MPH; Finkelstein SN, Stafford RS (2006). Off-label Prescribing Among Office-Based Physicians. *Arch Intern Med*. 166(9):1021-1026.
3. Blanco Reina E, Muñoz García A, Cárdenas Aranzana MJ et al (2017). Assessment of off-label prescribing: profile, evidence and evolution. *Farmacia Hospitalaria*, Vol. 41, N° 4
4. Danés I, Agustí A, Vallano A, Alerany C, Martínez J, Bosch JA, et al. Outcomes of off-label drug uses in hospitals: a multicentric prospective study. *Eur J Clin Pharmacol*. 2014;70(11):1385-93.
5. Egualé T, Buckeridge D.L, Verma A et al. (2016). Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern Med*. 176 (1):55-63
6. Vilhelmsson A, Davis C, Mulinari S (2016) Pharmaceutical Industry Off-label Promotion and Self-regulation: A Document Analysis of Off-label Promotion Rulings by the United Kingdom Prescription Medicines Code of Practice Authority 2003-2012. *PLoS Med* 13(1): e1001945. doi:10.1371/journal.pmed.1001945
7. Article 83 of Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. OJ L 136, 30.4.2004
8. Article 5 (1). Directive 2001/83/EC on the Community code relating to medicinal products for human use. OJ L 311, 28.11.2004
9. Weda M, Hoebert J, Vervloet M et al (2017). See reference 1
10. Real Decreto 1015/2009, de 19 de junio, por el que se regula la disponibilidad de medicamentos en situaciones especiales. BOE, núm. 174. 20.7.2009
11. ANSM (2012). Temporary Recommendation for Use (RTUs). Principles and information on the methods used by the ANSM for establishment and implementation. Agence Nationale de Sécurité du Médicament et des Produits de Santé.
12. G-BA (2018) Arzneimittelrichtlinie. Available at www.g-ba.de/downloads/62-492-1660/AM-RL_2018-05-17_iK_2018-09-15-AT-09-08-2018-B4.pdf

13. G-BA (2018) Arzneimittelrichtlinie Anlage VI. Available at www.g-ba.de/informationen/richtlinien/anlage/15/
14. Weda M, Hoebert J, Vervloet M et al (2017). See reference 1
15. World Medical Association (2018). Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. World Medical Association, 9 July 2018 (<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>)
16. Windeler J, Lauterberg J, Wieseler B et al (2017). Patient registries for benefit assessments—No replacement for randomized trials. *Dtsch Arztebl* 2017; 114(16): A-783 / B-662 / C-648
17. Health Action International. Direct Patient Reporting in the European Union . A Snapshot of Reporting Systems in Seven Member States. Health Action International, Amsterdam
18. Neville S (2012). GlaxoSmithKline fined \$3bn after bribing doctors to increase drugs sales, *The Guardian*, 3 July 2012 (<https://www.theguardian.com/business/2012/jul/03/glaxosmithkline-fined-bribing-doctors-pharmaceuticals>, accessed 5 October 2018)
19. Vilhelmsson A, Davis C, Mulinari S (2016). See reference 6
20. Zetterqvist AV, Merlo J, Mulinari S (2015). Complaints, Complainants, and Rulings Regarding Drug Promotion in the United Kingdom and Sweden 2004–2012: A Quantitative and Qualitative Study of Pharmaceutical Industry Self-Regulation. *PLoS Med* 12(2): e1001785. <https://doi.org/10.1371/journal.pmed.1001785>
21. Zetterqvist AV, Merlo J, Mulinari S (2015). See reference 20
22. Health Action International (2017). *Pharmaceutical Marketing: Report on Education on Pharmaceutical Promotion in Medical Training*. Health Action International, Amsterdam
23. ANEMF (2017). Communiqué de presse. Les facultés de médecine peuvent désormais adopter une charte éthique. Association Nationale des Étudiants en Médecine de France, November 2017. Available at <https://www.anemf.org/blog/2017/11/16/cdp-les-facultes-de-medecine-peuvent-desormais-adopter-une-charte-ethique/>
24. Health Action International et al (2017). Joint Submission to European Commission Public Consultation on Horizon 2020. 2 February 2017. Available at <http://haiweb.org/wp-content/uploads/2017/02/H2020-Joint-Submission-1.pdf>
25. Italian Medicines Agency. The independent research on drugs. [Online] <http://www.aifa.gov.it/en/content/independent-research-drugs>, accessed in September 2018
26. Liberati A, Traversa G, Moja LP, Trota F (2010). Feasibility and challenge of independent research on drugs: the Italian Medicines Agency (AIFA) experience. *Eur J Clin Invest* 2010, 40 (1): 69–89
27. Belgian Healthcare Knowledge Center (KCE). History and Objectives. What is KCE Trials? [Online] <https://kce.fgov.be/en/content/what-is-kce-trials>, accessed in September 2018
28. Neyt M, Christiaens T, Demotes J et al. (2016). Publicly funded practice-oriented clinical trials: of importance for healthcare payers. *J.Comp.Eff.Res.* 5(6), 551–560
29. Anticancer Fund. *Repurposing drugs for cancer treatment: Unlocking the potential*. (https://www.anticancerfund.org/sites/default/files/attachments/policy_paper_on_repurposing.pdf)



This document received funding under an operating grant from the European Union's Health Programme (2014–2020). Its content represents the views of Health Action International only and is the organisation's sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency, or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.