EUCOPE
European Confederation of
Pharmaceutical Entrepreneurs AISBL

EUCOPE
Position Paper on Government Induced Off-label Use as a Cost-Containment Measure

1. Executive summary

EUCOPE is concerned about recent regulatory changes in some EU Member States, which encourage off-label use of medicinal products with the sole aim of reducing public health expenditure. The comprehensive and stringent EU rules on marketing authorisation procedures for medicinal products safeguard patients' safety against the misuse of medicines. We believe that recent legislative developments across Member States threaten to undermine the robust approval system for medicinal products and could have critical implications for public health.

EUCOPE therefore considers it vital that:

- All players in the healthcare sector as well as the governments of the Member States strictly follow the legislation in place to safeguard a high level of public health.
- The prescription of medicines off-label should be limited to situations where no authorised forms of treatment are available or have failed.
- Physicians' duty of professional conduct towards their patients is not jeopardised by legislation or administrative practices imposed on them for the sole purpose of cost-containment.
- Additional measures are put in place to ensure appropriate pharmacovigilance in the context of the off-label prescription and administration to maintain the highest levels of patient safety.

2. Respect for the EU Regulatory Framework on medicinal products

The EU is empowered by Article 168(4c) of the Treaty on the Functioning of the EU (TFEU) to adopt binding legislation to "*set high standards of quality and safety for medicinal products and devices for medical use*".

The EU made use of its competence in this sector in particular by adopting Directive 2001/83/EC and Regulation (EC) No 726/2004, which lay down the requirements and procedures for the marketing authorisation of medicinal products for human use, as well as the rules for the constant supervision of products after they have been authorised.

The protection of public health is a core principle of the EU legislation in this sector, as recognised by Article 168(1) of the TFEU and by EU case law.

The cornerstone of the respective EU legislation is Paragraph 1 of Article 6 of Directive 2001/83/EC, which states that "*no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State*". The Directive also clearly outlines the strict procedures to which medicinal products are subject in order to test and assess their quality, efficacy and safety before being authorised.

Off-label use under EU law

EU legislation in the field of medicines for human use, including Directive 2001/83/EC, does not explicitly mention or define off-label use. However, the definition of off-label use given by Directive 2001/82/EC on veterinary medicines could be applied to human medicines as well:

"the use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics, including the misuse and serious abuse of the product".[1]

In addition, Annex I of the Guidelines on good pharmacovigilance practices – GVP (Rev. 3) provided by the European Medicines Agency and Heads of Medicines Agencies refers to off-label as

"*situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information"*.[2]

The law also contains certain exceptions from the marketing authorisation requirement. While not explicitly mentioned, off-label use may be allowed as an exception to compliance with Directive 2001/83/EC in order to:

1. "*fulfil special needs, […] in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by his individual patient on his direct personal responsibility*".[3]
2. Respond to health threats due to pathogenic agents, toxins, chemical agents or nuclear radiation;[4]
3. Allow compassionate use for groups of patients, when no other authorised medicinal product is available.[5]

These exceptions must be interpreted in a restrictive way to avoid undermining the ratio of EU legislation in this sector (see below).

3. Off-label: an unacceptable and unsafe cost-containment measure

As mentioned above, Article 5 of Directive 2001/83/EC suggests that in certain cases a physician may prescribe a medicine off-label. However, according to the provision itself, these cases are limited to the identification of special medical needs of the patient, as carefully assessed by the physician himself on a case-by-case basis. These elements clarify that off-label prescribing should remain an exception to the general rule motivated solely on the proven medical interest of the patient. These cases are thus limited to situations where there is no authorised medicine to treat the disease or there is another unmet medical need. **In all other cases, off-label use of medicines exposes the patient to unnecessary risks related to the safety and efficacy of the medicine.**

This was confirmed in the Judgment of Court of Justice of the European Union of 29 March 2012, European Commission v Republic of Poland.[6] In this case, a provision included in the Polish law on medicinal products, allowed the placing of imported generic medicinal products on the Polish market, although the generic did not have a marketing authorisation in Poland but only in other countries. The requirement was that the price of the imported medicine was lower compared to those that had a marketing authorisation.

The Court of Justice of the European Union found that the provision in the Polish law was in breach of Directive 2001/83/EC.[7] In its ruling, the Court of Justice of the European Union **ruled that financial benefits cannot prevail medical rationale in the prescription of off-label medicines.** The Court clearly stated that "*Article 5(1) of the directive cannot […] be relied on to justify a derogation from the requirement for a marketing authorisation for reasons of a financial nature"*.[8]

---

[1] Paragraph 16 of Article 1of the Directive 2001/82/EC.
[2] Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 3), EMA/876333/2011, dated on 15 April, 2014, p. 14, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf.
[3] Article 5 of the Directive 2001/83/EC
[4] "In response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm" as stated in Article 5 of the Directive 2001/83/EC.
[5] According to Paragraph 2 of Article 83 of Regulation 726/2004 *'Compassionate use'* […] for patient groups with life-threatening conditions that cannot be treated by an authorised medicinal product, but the product must be under application for a marketing authorisation […] or undergoing a clinical trial"..
[6] Judgment of Court of Justice of the European Union of 29 March 2012, European Commission v Republic of Poland, Case C-185/10.
[7] Judgment of Court of Justice of the European Union of 29 March 2012, European Commission v Republic of Poland, Case C-185/10, Line 50.
[8] Judgment of Court of Justice of the European Union of 29 March 2012, European Commission v Republic of Poland, Case C-185/10, Line 50.

In its judgement, the Court also stressed that "*Article 5(1) of Directive 2001/83 is not concerned with the organisation of the health-care system or its financial stability, but is a specific derogating provision, which must be interpreted strictly, applicable in exceptional cases where it is appropriate to meet special medical needs".*[9]

This position is in line with the overall obligation of EU legislation to put patients' health and safety first and conflicts with provisions that have recently been adopted by a number of EU Member States to promote off-label use in order to lower the cost of medicines in their health system. In this context, the same ruling stresses that Member States may not infringe the Directive when governing their national health-care insurance schemes (emphasis added): "*EU law does not detract from the power of the Member States to organise their social security systems and to adopt, in particular, provisions intended to govern the consumption of pharmaceutical products in order to promote the financial stability of their health-care insurance schemes, the* ***Member States must, however, comply with EU law in exercising that power****"*.[10]

It becomes clear that when national authorities encourage physicians to prescribe medicinal products off-label for purely economic reasons, regardless of the fact that there are approved medicines for that specific indication, they not only exceed their competences, they also undermine the EU regulatory framework for medicinal products.

4. Respect for the physician's duty to provide due care

Healthcare professionals have a duty to ensure the safety of patients under their care. They must be able to provide care that is tailored to the individual needs to their patients. Instances where a government policy puts economic benefit ahead of patient safety are a threat to the healthcare professional's ability to carry out their duty towards patients. Governments and health authorities have a duty to provide patients with the appropriate information related to the clinical benefits and therapeutic equivalence of medicines that are recommended for use, **especially in the context of cost-containment or financial incentive schemes.**

This principle is reinforced in the context of a case brought by the Association of the British Pharmaceutical Industry (ABPI) against the Health Products Regulatory Agency,[11] concerning a financial incentive scheme introduced by the National Health Service in the UK. The scheme sought to reward physicians for prescribing specifically designated medicinal products, which were cheaper than other medicinal products in the same therapeutic class. In its ruling, the Court concluded that doctors must be able to maintain professional objectivity in prescribing medicines that meet the individual needs of their individual patients and should not be prejudiced to do because of recommendations or inducements of the competent public health authorities.

"However, it should be noted that, in order to ensure the effectiveness of Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ 1989 L 40, p. 8), ***professionals in the pharmaceutical industry****, whether or not the prescription of their medicinal products is subject to financial inducements,* ***must also be able to verify that the financial incentive scheme implemented by the public authorities is based on objective criteria and that there is no discrimination*** *between national medicinal products and those from other Member States (see, to that effect, Case C-229/00 Commission v Finland [2003] ECR I-5727, paragraph 39, and A. Menarini Industrie Farmaceutiche Riunite and Others, paragraph 28)."* [emphases added][12]

"Consequently, even though Directive 89/105 has as an underlying principle the idea of minimum interference in the organisation by Member States of their domestic social security policies (Case C-245/03 Merck, Sharp & Dohme [2005] ECR I-637, paragraph 27), ***national public health authorities*** *which adopt a financial incentive scheme for the prescription of specific named medicinal products* ***are required*** *in particular to make such a scheme public and* ***to make available to health-care professionals and professionals in the pharmaceutical industry the evaluations***

[9] Judgment of Court of Justice of the European Union of 29 March 2012, European Commission v Republic of Poland, Case C-185/10, Line 48.
[10] Judgment of Court of Justice of the European Union of 29 March 2012, European Commission v Republic of Poland, Case C-185/10, Line 47.
[11] Judgment of the Court (Fourth Chamber) of 22 April 2010, ABPI v HPRA, Case C-62/09,.
[12] Judgment of the Court (Fourth Chamber) of 22 April 2010, ABPI v HPRA, Case C-62/09, Line 37.

establishing the therapeutic equivalence of the active substances available belonging to the therapeutic class covered by that scheme*." [emphases added]*[13]

5. Off-label: liability & risks to appropriate pharmacovigilance

Once placed on the market, all medicinal products are subject to continuous monitoring to ensure their quality, efficacy and safety. This process, known as pharmacovigilance, is regulated in the EU in particular by Directive 2010/84/EU, whereby, the marketing authorisation holder is obliged to report any noxious and unintended effect from the use of the medicinal product, including uses outside the terms of the marketing authorisation[14].

Despite this clear legislation, the lack of effective pharmacovigilance in the case off-label prescription continues to be an area of primary concern. Various studies have demonstrated that there is a lower level of reporting in the case of off-label medicines compared to on-label ones.[15]

The liability of the physician or healthcare professional prescribing and administering medicines off-label should be highlighted. It is widely recognised, in fact, that physician's responsibilities are enhanced if the prescription is for off-label use. If the patient had not been clearly informed and had not given is explicit consent to treatment off-label, and/or if the off-label use causes injury to the patient, the physician is not only exposed to civil liability claims for fault, but possibly also to criminal sanctions.[16] Because of this, physicians may be reluctant to report adverse events related to the prescription of a medicine off-label, which creates additional risks for patients as it hinders the pharmacovigilance process.

Dr. Alexander Natz
Secretary General

Dr. Oliver Sude
Legal Counsel

[13] Judgment of the Court (Fourth Chamber) of 22 April 2010, ABPI v HPRA, Case C-62/09, Line 38.
[14] Directive 2010/84/EU
[15] For more information see Off-label prescription: Practice and problems, Portuguese Journal of Cardiology, 22 December 2012.
[16] See Off-label use of medicinal products and product liability, Practical Law Company, 2013.