

Cost considerations should not drive off-label drug use in the EU

With off-label drug use in the EU moving into the regulatory spotlight, it is becoming clear just how limited member states are in their power to stimulate – or indeed allow – the practice.

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Off-label use of medicines always used to be somewhat in the shadows in terms of pharmaceutical legislation and there were almost no discussions at EU level on the conditions under which it should be permitted. At national level, there have been treatment guidelines, general professional recommendations and reimbursement decisions or recommendations, but these only provide partial and often ad hoc regimes. More recently, however, various EU developments have brought the topic to the fore and provide some elements of more common EU principles.

The core principle of EU pharmaceutical legislation is that the interests of public health and the medical needs of the patient take precedence. This principle is long established and also applies to off-label use of medicines. Recent legal developments now further demonstrate that official institutions are not entitled to stimulate off-label use of medicines for financial reasons. These developments are discussed in this article.

There are of course also important developments at the national level. In France, for instance, law No 2011-2012 of 29 December 2011 inserts specific provisions on off-label use in the Public Health Code and in the Social Security Code. National developments are not discussed in this article.

The concept under EU law

The EU rules governing medicines for human use, in particular Directive 2001/83/EC, do not include a definition of off-label use of medicines¹. The veterinary medicines directive (Directive 2001/82/EC), however, defines off-label use as:

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 product².

As the regulatory regime for human use medicines is very similar to that governing veterinary medicines, it is possible to apply this definition by analogy to all medicines.

Uses that are “not in accordance with the summary of product characteristics” (SmPC) can of course be very different in nature. The most striking example is the use of a medicine for a therapeutic indication that is not only different from, but totally unrelated to, the therapeutic indication for which the product is approved (and which is reflected in the SmPC).

A typical and much debated example is the use of Roche’s Avastin (bevacizumab), which is approved for various oncology indications, but is used off-label in the treatment of wet age-related macular degeneration (AMD).

It is of course possible that the use is for an unapproved therapeutic indication, but that indication is medically related to the approved indication. This may occur rather frequently in the oncology sector: Carboplatin medicines, for instance, are indicated for small cell lung carcinoma but are also used for advanced non-small cell lung carcinoma; and doxorubicin, which is approved for various oncology indications, is also used more widely, such as for Merkel cell carcinoma.

For a long time, EU rules have made it clear that making a medicine available for off-label use must remain exceptional

Other examples of off-label use are the use within an approved indication but for a different patient group or under different conditions. These examples may be less drastic but can still be very relevant from a public health point of view. For instance, the absence of reliable data on the paediatric use of many medicines resulted in the adoption of the Paediatrics Regulation (Regulation (EC) No 1901/2006³), which combines a paediatric obligation (the need to have a paediatric development approved, and in principle implemented, for new medicines or important variations to existing products that are still under patent or protected by a supplementary protection certificate) with a paediatric reward (six-month extension of the SPC or an additional two years of market exclusivity for orphan medicines)^{4,5}.

The wide scope of this relatively new regime and the amount of resources and time dedicated by regulatory authorities (especially the Paediatric Committee within the European Medicines Agency) and companies to preparing, reviewing, implementing and adjusting paediatric development plans illustrate the importance of this type of off-label use that very frequently occurred in the past.

EU pharmaceutical law does not directly regulate off-label use of medicines. In general, it only regulates products and not the way the products are ultimately used in medical

practice. This also reflects the limited powers in general in the field of health. Article 168 of the Treaty on the Functioning of the EU (TFEU)⁶ specifically empowers the EU to adopt binding legislation that “set[s] high standards of quality and safety for medicinal products and devices for medicinal use” but adds that all EU action must “respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care”. Article 168 (7) adds that “[t]he responsibilities of the Member States shall include the management of health services and medical care and the allocation of resources to them.”

On the other hand, Article 168 (1) states that “a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities”. The CJEU has also recognised that the protection of health is the overriding principle underpinning the EU pharmaceutical rules. For instance, in *Artegodan*, the Court of First Instance ruled that there is a “general principle, identified in the case-law, that protection of public health must unquestionably take precedence over economic considerations”⁷.

These principles mean that it remains open on whether the EU is empowered to directly and comprehensively regulate off-label use but is at least expressly entrusted with the task of ensuring the quality and safety of medicines, through strict measures, which obviously must also take into account the actual use of the product. This is also reflected in the more recent developments in EU pharmaceutical law that show a growing focus on off-label use (see below). For a long time, however, the EU rules have made it clear that making a medicine available for off-label use must remain exceptional. This is illustrated by the following elements:

- The general rule is that a medicine can only be placed on the market when it benefits from a marketing authorisation, which is granted after a thorough review of all the data that relate to the quality of the product and its safety and efficacy in the intended use. The decision includes the SmPC, one of the core parts of which are the description of the therapeutic indication and the posology and method of administration.
- A medicinal product can only be promoted

when it is covered by a marketing authorisation and all promotion must “comply with the particulars listed in the summary of product characteristics”. The CJEU has held that these rules not only apply to the pharmaceutical company marketing the product but, in principle, to all persons because “even where it is carried out by an independent third party outside any commercial or industrial activity, advertising of medicinal products is liable to harm public health...”⁸.

- There are very limited exceptions to the marketing authorisation requirement in Directive 2001/83/EC⁹. Article 3 exempts magistral and officinal formulas and Article 5(1) contains the exception for named patient sales. Although it is interpreted rather flexibly as to the specific procedures¹⁰, the core requirements are that there is a need to “fulfil special needs”, that the order is unsolicited and that the use occurs under the direct responsibility of a healthcare professional. As with all exceptions, this possibility should also be interpreted rather restrictively. This was recently confirmed by the CJEU in *Commission v Poland* which is discussed below.
- Article 5 (2) and (3) of Directive 2001/83 further allows the marketing of authorised medicines in case of an emergency, such as a pandemic, and stipulates that healthcare professionals should not incur civil or administrative liability for use of an unauthorised medicine or use “otherwise than for the authorised indications” if the use was recommended or required by authorities in response to an emergency. These principles clearly demonstrate that off-label use must remain exceptional and should be dictated by medical need (and, of course, also be based on informed consent¹¹).

Finally, the EU regulatory regime also expressly recognises the need to stimulate innovation (in particular in terms of data exclusivity, also sometimes extended to new indications, under Article 10 of Directive 2001/83, and the extension of patent protection under the SPC Regulation (469/2009) and the Paediatrics Regulation). The regime strikes a delicate balance between the need to stimulate innovation, on which the further improvement of healthcare depends, and controlling official healthcare spending, in particular by stimulating the availability of generic medicines. This balance should not be undermined by allowing off-label use for other reasons than patient needs.

Recent developments in EU law

The EU regulatory regime for pharmaceuticals is currently giving more attention to off-label

use. A significant development, for instance, is the package of new pharmacovigilance rules that was adopted in December 2010^{12,13}.

The new rules now make it very clear that the term “adverse reaction” also covers off-label use. Recital 5 to Directive 2010/84, for instance, states that the amendment ensures that the term “covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation”. As to the general reporting obligations of the marketing authorisation holder, Recital 12 states that “[a]s medicinal products could be used outside the terms of the marketing authorisation, the marketing authorisation holder’s responsibilities should include providing all available information, including ... any use of the medicinal product which is outside the terms of the marketing authorisation”¹⁴.

National social security measures must not only avoid directly infringing the EU pharmaceutical rules; they also must respect the practical effectiveness of these rules

In addition, the definition of a post-authorisation safety study (PASS) is now broadened and is not limited any more to a study “carried out in accordance with the terms of the marketing authorisation”. This means that regulators can now require companies to conduct a PASS that also covers off-label use (but that broad scope is not envisaged for post authorisation efficacy studies).

The 2010 pharmacovigilance revision also amends the grounds for a suspension, revocation, withdrawal or variation of a marketing authorisation. This is now possible under Article 116 when, for instance, the risk-benefit balance is not favourable (the earlier version referred to the risk-benefit balance not being positive “under the normal conditions of use”). Similar principles now apply under Article 117 of the directive.

A second development is the recent proposal for a new transparency directive that mainly sets procedural requirements for national pricing and reimbursement decisions¹⁵. Article 1(3) of the current transparency directive (Directive 89/105/EEC¹⁶) provides that:

[n]othing in this Directive shall permit the marketing of a proprietary medicinal product in respect of which the authorization provided for in Article 3 of Directive 65/65/EEC has not been issued.

This is the mirror provision of Article 4(3)

in Directive 2001/83/EC. Together, the two provisions firmly establish the mutual independence of the marketing authorisation procedures and pricing and reimbursement procedures, which also implies that one regime should not undermine the other.

This is now strengthened by the proposal for a new transparency directive, replacing Directive 89/105/EEC. The proposal maintains the existing Article 1(3), but with the necessary technical updating so that it now reads:

Nothing in this Directive shall permit the placing on the market of a medicinal product which has not received marketing authorisation as provided for in Article 6 of Directive 2001/83/EC.

It also includes a new Article 13, which states:

In the framework of pricing and reimbursement decisions, Member States shall not re-assess the elements on which the marketing authorisation is based, including the quality, safety, efficacy or bioequivalence of the medicinal product.

This is specifically intended to avoid delays in pricing and reimbursement decisions for generic medicines, based on concerns related to bioequivalence or other aspects affecting the safety or efficacy of the product. Recital 14 of the proposed new directive states:

The quality, safety and efficacy of medicinal products, including the bioequivalence of generic medicinal products with the reference product, are ascertained in the framework of marketing authorisation procedures. In the framework of pricing and reimbursement procedures, Member States should therefore not re-assess the elements on which the marketing authorisation is based, including the quality, safety, efficacy or bioequivalence of the medicinal product.

It also, however, expresses a more fundamental need for pricing and reimbursement authorities to respect the marketing authorisation system and to refrain from actions that undermine it.

Sincere co-operation obligation

Taking into account the elements discussed above, the limits of the powers of member states to allow, and especially to stimulate, off-label use are becoming clearer. They are fundamentally based on the obligation of member states to provide sincere co-operation with and active loyalty towards EU law in general, laid down in Article 4.3 of the Treaty on European Union (TEU)¹⁷.

Under these basic EU law principles, national social security measures must not only avoid directly infringing the EU pharmaceutical rules; they also must respect the practical effectiveness (effet utile) of these rules and, in

particular, of the essential elements, such as the marketing authorisation requirement under Directive 2001/83.

This obligation applies to public authorities and other bodies that perform a public service. The CJEU has adopted a broad interpretation of what entities are subject to the loyalty obligation under Article 4.3 of the TEU. In *Von Colson and Kamann* (Case 14/83), it held that the obligation is "binding on all the authorities of a Member State including, for matters within their jurisdiction, the courts" (para 26).

In *Thieffry* (Case 71/76), the court applied the obligation of sincere co-operation to "the practices of the public service or of professional bodies" (para 17) and "public authorities, including legally recognised professional bodies" (para 18) such as the local bar authorities.

This means that all national or regional entities that perform a public function in the context of pricing and reimbursement of medicines must refrain from activities that undermine the marketing authorisation system. Applied to off-label use of medicines, this means that there must be no active support for or endorsement of off-label use unless it is based on specific medical patient needs. The logical consequence is that promoting or supporting off-label use for financial reasons is not permissible.

Commission v Poland

This conclusion is fully in line with the very recent decision by the CJEU in *Commission v Poland*^{18,19}. That case concerned a national measure in Poland, allowing named patient imports of medicines that have the same active ingredient, dosage and pharmaceutical form as products with a marketing authorisation in Poland, provided the imported product has a "competitive price." This was held invalid as a financial criterion cannot justify an exemption from key elements of Directive 2001/83. The CJEU's advocate general stated in his opinion:

The aim of Directive 2001/83 is to safeguard public health as well as to ensure that trade is not affected in the market for medicinal products. (8) In my view, the harmonised marketing authorisation procedure is a precondition for access to the market for medicinal products in the European Union, and is the cornerstone of that directive. It enables cost-efficient and non-discriminatory market access, while ensuring that the requirements of safeguarding public health are achieved through meticulous and uniform scrutiny of the pharmaceutical and medicinal properties of the product in question. (para 19)

The court confirmed this statement and held: ... the possibility of importing non-approved medicinal products, provided for under national

legislation implementing the power laid down in that provision, must remain exceptional in order to preserve the practical effect of the marketing authorisation procedure ... (para 32)

and
It is apparent from the conditions as a whole set out in Article 5(1) of Directive 2001/83, read in the light of the fundamental objectives of that directive, and in particular the objective seeking to safeguard public health, that the derogation provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market. Where medicinal products having the same active substances, the same dosage and the same form as those which the doctor providing treatment considers that he must prescribe to treat his patients are already authorised and available on the national market, there cannot in fact be a question of 'special needs', within the meaning of Article 5(1) of Directive 2001/83, necessitating a derogation from the requirement for a marketing authorisation under Article 6(1) of that directive. Financial considerations cannot, in themselves, lead to recognition of the existence of such special needs capable of justifying the application of the derogation provided for in Article 5(1) of that directive. (para 36 to 38)

Measures that stimulate or promote off-label use of medicines must reflect concrete medical needs of the patients

The same considerations logically apply to measures that stimulate or promote off-label use of medicines. They cannot be based on financial reasons but must reflect concrete medical needs of the patients. Otherwise, the practical effect of the marketing authorisation system established by EU law, as well as the delicate balance of measures aimed at stimulating innovation, is undermined.

Conclusion

For a long time, off-label use of medicines remained in the shadow of EU pharmaceutical law. The EU rules have, however, significantly evolved over the years and give increasing attention to how products are actually used in medical practice. In addition, basic EU law principles are now more frequently applied by the CJEU in the pharmaceutical context and their impact is clarified.

These developments make it clear that the predominant considerations for off-label use of medicines must be the medical needs of the

patient and the protection of patient rights. They also show that official bodies are only entitled to support or promote off-label use when this meets medical needs, and that they are not entitled to do so for financial reasons.

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