The need for informed consent in off-label use in the EU

Cándido García Molyneux and *Peter Bogaert* explain the informed consent requirements for off-label use in the EU and discuss the potential for physician liability.

The off-label use of medicinal products has always been a sensitive topic. The entire EU medicines approval system is based on providing a clear and, to the extent possible, comprehensive description of how a specific medicinal product can be used. This is laid down in the marketing authorisation, which includes a summary of product characteristics (SmPC) that is used as a concrete guideline for doctors on how to prescribe and use the medicine.

For many reasons, however, there may be a need to use a product outside the specifications laid down in the SmPC. There will always remain gaps in approvals and especially in light of individual patient needs, off-label use will often play a role in medical treatment. That use will primarily be based on the professional opinion of the treating doctor, but it is also important to recognise the role of patients. Patients have a fundamental right to be informed about the treatments they receive and to be put in a position to actively participate in the treatment decisions.

This article addresses the informed consent requirement in off-label use, also in light of possible liability for the doctor. It does this mainly on the basis of the legal situation in Italy and Spain, which explicitly regulate off-label use, but also adds some elements from EU law principles and other EU member states where off-label use is not statutorily regulated.

What is off-label use?

There is no definition of off-label use in the EU legislation on human medicines. Since 2000, however, the rules on veterinary medicines have defined the term as[1]: "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." [emphasis added]

For human medicines, off-label use often takes place in specialised fields such as oncology and paediatrics, but it can also occur in more general types of applications. That use is almost always based on less reliable data, and there is a preference to then further develop the product to have the off-label uses ultimately addressed (either way) in the SmPC. For example, in the context of paediatric use of medicines, the Paediatrics Regulation ((EC) No 1901/2006) provides a systematic regulatory approach to address the need for positive or negative data on how medicines can be used in children[2].

The ultimate goal is, thus, to cover the gap in the approvals through new data. Sometimes, at the product-specific level, the need to fill that gap is taken into account in the approval process. For instance, the need for having an approved systemically active medicine for the treatment of rosacea was considered by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) when it issued a positive opinion following a referral for Oracea under Article 29(4) of Directive 2001/83/EC on human medicines[3]:

> *In assessing the benefit/risk of Oracea, the current situation of limited treatment options for rosacea was taken into consideration, as well as the fact that Oracea is expected to provide an alternative to the international guidelines recommending off-label use of Doxycycline (or other tetracycline derivates) for the treatment of rosacea, with the associated decrease in risk for adverse events. Thus, the CHMP considers that the benefits of marketing a systemic drug such as Oracea in the present indication outweighs the risk for potential harmful effects related to resistance development and therefore consider the benefit-risk ratio to be positive.*[4]

Sometimes marketing authorisations also include measures aimed at controlling off-label use. When the European Commission approved Revolade (eltrombopag) for the treatment of certain forms of thrombocytopenia in March 2010 – in particular for adult chronic immune (idiopathic) thrombocytopenic purpura splenectomised patients who are refractory to other treatments (eg corticosteroids), and possibly as second line treatment for adult non-splenectomised patients where surgery is contraindicated – the marketing authorisation included strict requirements for information programmes by prescribing doctors.

A look at variations

In practical terms, defining off-label use as "not in accordance with the SmPC" is the most convenient way to conceptualise the activity, but it can of course include practices ranging from detailed deviations from the prescribing information to significant changes, including even reformulation of the product.

This broad range can be compared with the various types of amendments to a marketing authorisation and the different procedures that apply to them under the EU rules governing variations[5]. They include simple administrative changes (typically classified as minor type IA variations), more substantive changes (minor type IB variations – typically certain manufacturing changes or restrictions in the SmPC, like deletion of a therapeutic indication) and major variations (such as addition of a new therapeutic indication, inclusion of a new target population, posology changes, etc). Most off-label uses correspond to major variations, which require express prior approval.

There is another category of changes to an existing marketing authorisation that are considered so significant that they require approval through a separate marketing authorisation procedure. These are "extensions of marketing authorisations" and they include changes in strength, pharmaceutical form or route of administration. Occasionally, off-label use can correspond to such "extension" if it also involves reformulation or different formulation of the product.

Looking at the variations rules can be useful in assessing when off-label use is acceptable

The analogy between off-label use and the EU variations rules is expressly recognised in the Medicines Instructions (*Arzneimittelrichtlinien*) issued by the German Federal Joint Committee in the context of the national healthcare reimbursement rules. The instructions define off-label use (called "use beyond the marketing authorisation") as any use "in indications or indication areas" not covered by the authorisation, as well as "any use that justifies a variation of the marketing authorisation".

Conceptually, the analogy with the variations rules can provide a useful element in assessing the conditions under which off-label use can be considered acceptable. Among other things, this is relevant to the need for consent and the scope of the prescribing doctor's liability.

The latter is also in line with the EU rules governing another exception to the general principle of marketing authorisation, named patient sales. Article 5(1) of Directive 2001/83/EC permits member states to allow named patient sales of unapproved medicines "to fulfil special needs", where the product is "supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility".

The following sections of this article examine in more detail the requirement of consent by the patient and the scope of

liability of the prescribing doctor when a medicine is prescribed off-label.

Informed consent: a fundamental right

While the EU pharmaceutical rules do not regulate off-label use, and, for instance, do not explicitly require the patient's informed consent, such consent is now a European right that all EU member states are bound to protect.

Informed consent is part of a new paradigm in the relationship between doctors and their patients. It reflects a move from a hierarchical relationship, where the doctor has all the power of decision and the patient plays a passive role, to a modern and more horizontal relationship, where the patient is the "main character" and has basic rights. Informed consent is the means to ensure that the beliefs of the doctor and other practical considerations do not override the right to freedom and personal integrity of the patient[6].

This is also generally recognised by the new legislative initiative on pharmacovigilance, which is near adoption, and that on information to patients, which is pending in the European Parliament and the Council of Ministers[7]. It is further reflected by the increasing role of patient organisations in the regulatory process.

Informed consent has become a European fundamental right. The Council of Europe's Convention on the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Oviedo Convention) requires the informed consent of the patient for any medical treatment[8]. On this basis (and despite the fact that not all member states have ratified the convention), the European Court of Human Rights has held that failure to protect the right to a "free, express and informed" consent, as set out in Article 5 of the convention, constitutes a violation of the right to "private life" of the European Convention on Human Rights[9], to which all EU member states are bound.

Similarly, the Charter of Fundamental Rights of the European Union (European Charter) provides that in the field of medicine, "the free and informed consent of the person concerned", must be respected, according to the procedures laid down by law[10]. This right is binding on EU institutions and also on EU member states when they implement EU law, such as EU pharmaceutical law.

The requirement of informed consent under the Oviedo Convention and the European Charter applies to any medical treatment. It is even more relevant when patients receive a specific treatment that deviates from the details of the marketing authorisation, especially because the risks are much less well-established in off-label use. Therefore, the benefit:risk considerations that doctors and patients must take into account when deciding to prescribe off-label use are largely dependent on individual risk factors.

For off-label use, informed consent means that the patient has adequate information on the available treatments (both off-label and "on-label" uses), including the risks and benefits as best known. The patient must explicitly provide consent to the off-label treatment.

The obligation to obtain the informed consent of the patient when engaging in off-label use is increasingly highlighted in different legal jurisdictions across Europe. Furthermore, it is reflected in case law across Europe that establishes that doctors and their health institutions may be held liable if they fail to obtain the informed consent of the patient. This case law suggests that failure to obtain the informed consent of the patient when engaging in off-label use constitutes a violation of the duty of medical care – also referred to as *lex artis* – that doctors owe to their patients.

Informed consent in Italy

Italian legislation explicitly highlights the importance of obtaining the patient's informed consent to legitimise the off-label use of medicinal products. Article 3(2) of Law 94 of 1998 *(Legge di Bella)* provides:

> *…in single cases, the doctor may, under his own direct responsibility, and after informing the patient and obtaining his consent, use an industrial medicinal product for an indication or means of administration or form of administration or of use different to that authorized […] if the doctor considers, on the basis of documented data, that the patient cannot be treated with medicinal products for which there is an approved therapeutic indication or means or form of administration and provided that such use is known and in accordance with research published in internationally reputable scientific publications.*

An Italian Supreme Court decision clarifies that Article 3(2) of the *Legge di Bella* requires three conditions for off-label use to be valid: the informed consent of the patient has to be obtained; it is deemed impossible, on the basis of documented data, to treat the patient "on label"; and the off-label use must be known and in accordance with research published in internationally reputable scientific publications[11].

Law 244 of 2007 (*Legge Finanziaria 2008*) goes even further by adding that the doctor's decision must be based on data resulting from Phase II clinical trials.

The right to informed consent in Italy ultimately derives from two basic fundamental rights enshrined in the Italian Constitution: "the inviolability of personal liberty" and "the right of each individual to health care as well as not to be forcefully submitted to medical treatment except as regulated by law".[12] The Italian Constitutional Court has confirmed this[13] and the Ethics Code of the Italian National Federation of Medical Orders also makes clear that a doctor may not engage in any diagnostic or therapeutic activity without the explicit and informed consent of the patient[14].

Italian civil and criminal courts have emphasised the importance of the patient's informed consent in case law that increasingly reflects a change in Italian society's perception and expectations of doctor-patient relationships[15]. This case law suggests that doctors will only have complied with the *lex artis* – and thus will avoid liability associated with the treatment of their patient – if they have obtained the patient's informed consent.

Italian doctors may be held criminally liable for failing to obtain informed consent

Doctors who do not obtain a patient's informed consent when prescribing off-label use of a medicinal product may be subject to disciplinary proceedings before the ruling bodies of the relevant medical orders, whose decisions may be appealed to the Supreme Court[16]. A medical order may hold a doctor responsible both if it finds that the patient received insufficient information about the off-label treatment option and if the patient is injured as a result of that treatment.

Furthermore, civil courts will accept claims for damages if the doctor failed to properly inform the patient and obtain consent. However, claimants will only be successful if they can show that they suffered harm as a result of the doctor's failure to properly inform them about a given therapeutic treatment[17].

The Italian Supreme Court has addressed the criminal liability of doctors when they engage in off-label use without the informed consent of the patient[18]. The case concerned a psychiatrist's off-label use of Topamax (topiramate), which was authorised for the treatment of epilepsy, to treat a minor for obesity. The doctor prescribed Topamax without first trying other available treatments and without the informed consent of the parents. Furthermore, the doctor did not sufficiently monitor the patient for possible side effects, even as he increased the dosage, despite the fact that parents alerted him of the significant adverse effects of the product.

The court confirmed that in order to be legitimate, the practice of medicine, including off-label use, requires the patient's informed consent. Doctors may not engage in any

medical treatment without the consent of the patient. This must "be informed, that is expressed and following the provision of complete information, on the part of the doctor, of all the possible negative effects of the therapy of intervention, with an indication of the possible contraindications and the severity of the effects of the treatment". Furthermore, the consent includes "not only the possibility to decide between different medical treatments, but also of eventually refusing the therapy and knowledgably deciding to suspend it".

Notably, the Supreme Court also held that although the patient's informed consent is a prerequisite for the legitimate practice of medicine, criminal liability of the doctor requires more than the absence of consent. A separate element of negligence, related to having failed to avoid a foreseeable and avoidable harm, must be proven.

Informed consent in Spain

In Spain, Royal Decree 1015/2009 authorises doctors to prescribe off-label in exceptional circumstances if there are no authorised alternative therapies for the particular patient[19]. The decree repeatedly states that such off-label use requires the doctor to obtain the prior informed consent from the patient, in accordance with Law 41/2002.

In effect, Law 41/2002 emphasises the principle that all medical intervention in Spain must be based on the patient's prior informed consent. In particular, Article 4 of the law establishes the patient's right to be informed of all interventions concerning his health, including the intervention's nature and purpose, risks and consequences. Article 8, in turn, requires that all medical intervention be subject to the patient's "free and voluntary consent" on the basis of the information received in accordance with Article 4.

The Spanish Constitutional Court established that a patient's informed consent is an exercise of the "right of 'self-determination' that has as its object [the patient's] own body […] and that is based on the fundamental right of physical integrity" found in Article 15 of the Spanish Constitution[20,21]. The Supreme Court has further developed this idea by repeatedly holding that the patient's right to give his informed consent is "closely linked with the right of 'self-determination' […] that is characteristic of an advanced stage in the configuration of [the patient's] relation with the doctor"[22,23].

That right of self-determination was already reflected in the first main health law that was adopted under the Spanish Constitution – Law 14/1986 on Health (*Ley General de Sanidad*). The law required the Spanish public health system to provide patients with complete and continued information, written or oral, on their disease, diagnosis, prognosis and alternative treatments available. It further required that the information be provided to patients in a manner that they could understand.

Law 14/1986 has served as a basis for the long-standing case law of the Supreme Court on informed consent. Among other things, the court has held that while the doctor is not required to obtain the patient's informed consent in writing, a lack of written consent will place the burden of proving that the patient gave an adequate informed consent on the doctor and his health institution[24]. Furthermore, a generic informed consent form is not sufficient and the language must be "sufficiently concrete with respect to the chirurgical operation to which the patient will be subjected".[25,26]

Importantly, the Supreme Court has also made clear that failure to obtain adequate informed consent from the patient may result in civil liability for the doctor and administrative liability for the doctor's public health institution.

According to the court, in the patient-doctor (or health institution) relationship, patients are not entitled to receive a specific medical outcome, but they do have a right to treatment in accordance with the *lex artis*. The court has said that the informed consent of the patient "is an essential element" of the *lex artis*[27]. Therefore, failure to obtain such consent constitutes a violation of the *lex artis* that results in liability for the doctor and the public health institution, if there has been damage to the health of the patient[28]. Furthermore, most commentators take the position that failure to obtain the informed consent of the patient may also result in criminal liability for the doctor[29,30].

Other examples in the EU

Even in those European jurisdictions where off-label use is not explicitly statutorily regulated, doctors will be held liable if they engage in off-label use without the informed consent of the patient. For example, in the UK, current authoritative medical guidance will only support the off-label use of medicinal products if the doctor has obtained prior informed consent from the patient.

The UK General Medical Council's guidance on prescribing unlicensed medicines and off-label use provides that doctors "must give patients, or those authorising treatment on their behalf, sufficient information about the proposed course of treatment including any known side effects or adverse reactions", and, with respect to off-label in particular, "it is good practice to give as much information as patients, or those authorising treatment on their behalf, require or which they may see as significant. Where patients, or their carers express concern you should also explain, in broad terms, the reasons why medicines are not licensed for the proposed use".[31]

The Medicines and Healthcare products Regulatory Agency also provides advice for prescribers on the use of unlicensed medicines and off-label use[32], and states that "best practice is that you give patients, or those authorising treatment on their behalf, sufficient information about the proposed treatment, including known serious or common adverse reactions, to enable them to make an informed decision".

English courts have held that doctors must inform their patients of the risks of an off-label treatment in order to comply with the *Bolam* standard of duty of care[33], ie where a doctor is "not considered guilty of negligence if he has acted in accordance with the practice accepted as proper by a responsible body of medical men skilled in the particular art. […] Putting it the other way round, a doctor is not negligent if he is acting in accordance with such practice, merely because there is a body of opinion which takes a contrary view".[34]

Similarly, in France, doctors who prescribe off-label use of medicines will be held liable if they fail to inform their patients. This obligation to inform patients is confirmed in the *Code de la Santé Publique*, which states that doctors must seek the consent of their patients in "all cases". If the patient refuses the prescription, the doctor must respect the will of the patient.

In the words of the French Civil Supreme Court (*Cour de Cassation*)[35]: "[E]veryone has the right to be informed of the risk prior to investigations, treatments or preventive measures and the consent must be obtained by the doctor" and non-compliance with this obligation causes harm to the uninformed patient that "the judge may not leave without compensation".

For example, in 2008, the *Cour de Cassation* assessed the liability of a doctor who had prescribed the off-label use of the vasodilator papaverine to treat the erectile dysfunction of a patient, resulting in total and irreversible erectile dysfunction. The court held that the doctor was liable for harm suffered by the patient because he had failed to properly inform the patient that an emergency hospital service could have been consulted[36].

Conclusion

Off-label use will most likely continue to play a specific role in the treatment of patients in the coming years. This role may also further develop in light of medical and scientific developments, such as pharmacogenomics.

Off-label use, however, must be in line with the standard of good medical care, or *lex artis*,

that doctors owe to their patients. In most cases, this will require some independent professional validation of the envisaged off-label use, based on scientific publications or medical treatment guidelines by leading organisations. The latter should not, however, exempt the individual doctor from making his or her own professional assessment, taking into account all relevant factors of the individual case.

Our society's new perception of the doctor-patient relationship and the new fundamental rights enshrined in the European Charter and the Oviedo Convention entail that compliance with the standard of good medical care requires doctors to obtain the patient's explicit consent to off-label use. This informed consent of the patient is also very important in practical terms as the benefit:risk considerations that must be taken into account when deciding to prescribe off-label use are largely dependent on individual risk factors.

In order to be meaningful, the consent of the patient must be based on adequate information and cover at least the following elements: an indication of the fact that the envisaged use is off-label; information on possible alternative treatment "on label"; an indication of the possible risks of off-label use in general and of off-label use in the specific instance (in light of the disease and the specific characteristics of the patient); and the cost implications of off-label use, if relevant.

The patient's consent must be real, that is, the patient must have the real possibility to refuse the off-label use and be treated with an alternative treatment "on-label". Furthermore, the right to give an informed consent entails that where the doctor does not obtain the informed consent, this should be considered a failure to comply with the standard of good medical care, which may result in the civil, criminal and/or administrative liability of the doctor and his or her health institution.

In assessing the level of detail required for informed consent and the level of care needed for the selection of the therapy by the doctor, the variations rules for medicines can provide some general guidance. They indicate, for instance, that the use of a differently formulated product (eg different pharmaceutical form) requires more detailed review, even irrespective of the quality concerns that may arise in that case. This assessment must be supplemented, however, with a case-specific review of the envisaged off-label use, taking into account the disease and the individual characteristics of the patient.

In general, a decision to use a medicine off-label, and whether to obtain the informed consent of the patient, should not be based on cost considerations. The General Court of the EU made this clear when it confirmed the general principle that the "protection of public health must unquestionably take precedence over economic considerations" and applied this to marketing authorisation decisions[37]. The same principle logically also applies in the context of off-label use.

Finally, to the extent that national pricing and reimbursement rules address off-label use, member states must respect the principle of the Transparency Directive that national measures "should also be intended to promote efficiency in the production of medicinal products and to encourage research and development into new medicinal products, on which the maintenance of a high level of public health within the Community ultimately depends".[38]

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