Patients' Rights and Medical Liability within Off-Label Prescription

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Abstract
Off-label prescription refers to the use of a medication beyond what it is established in the respective Marketing Authorization (MA). This broad definition encompasses situations in which the drug was used for a therapeutic indication not authorized in the MA; with a different dosage or with a different frequency than those mentioned in the MA; introduced in the patient's body by a different procedure, not stated in the MA; or to a group of patients not specified in the MA.
The freedom of prescription is a defining note of the medical profession; therefore, the doctor has the power to choose which drug to use, even disregarding the content of the MA, provided the medical decision complies with medical leges artis.
However, when a drug is prescribed off-label this means that it is being used in a medical scenario for which it has not been specifically authorized (i.e., the drug was not submitted to clinical trials for that particular medical situation). Because of the lack of scientific evidences regarding the efficacy and safety of the drug the patient can suffer serious injuries and, consequently, the doctor and the pharmaceutical company are more susceptible of being sued.
This is the reason why it is of outmost importance to provide proper legal protection to patients' rights (namely, the right to inform consent) and to guarantee that the doctor acts for the benefit of patient's safety.

Keywords: off-label prescription, patient's rights, informed consent, medical liability, producer's liability

Introduction: Definition of off-label prescription

Every drug that enters into the market requires a proper Marketing Authorisation (MA), aimed to evaluate its safety, quality and efficacy (Feldschreiber, 2008: 103-110; Feldschreiber & Breckenidge, 2008: 3-21; Lisman & Schoonderbeek, 2005: 27-37; Permanand, 2006: 1-68; Raposo, 2014: 35-77; Rogers, 2008: 23-69).

The MA works as a kind of "identity card" for the drug. In fact, the drug's therapeutic indications, its frequency, dosage, route of administration and type of patients are set by the MA in accordance with the material submitted by the manufacturer for approval by the competent authorities. These indications are subsequently included in the Summary of Product Characteristics (SmPC) (Working Group of Nsw Tag Inc, 2003). In this sense, both documents – the MA and the SmPC – constitute the "script" that the doctor must follow when prescribing any drug.

However, sometimes they both are disregarded and the drug is used outside its label. Off-label prescription refers to the use of a medication beyond what it is established in the respective MA. This broad definition encompasses situations in which the drug is used for a therapeutic indication not authorized in the MA; with a different dosage or with a different frequency than those mentioned in the MA; introduced in the patient's body by a different procedure, not stated in the MA; or to a group of patients not specified in the MA.

When a drug is prescribed off-label this means that it is being used in a medical scenario for which it has not been specifically authorized, i.e., the drug was not submitted to clinical trials concerning that particular medical situation. Because of the lack of scientific evidences regarding the drug's efficiency and safety the patient can suffer serious injuries and, consequently, the doctor faces an increased risk of medical liability. This is the reason why it is imperative to issue adequate regulation to provide a legal framework to this practice in order to protect doctors from litigation and to protect patients from injuries.

Medical liability in off-label prescription

Off-label prescription does not necessarily violate medical *legis artis* (Kon, Iličkovi & Mikov, 2015; Ma & Lou, 2013; Raposo, 2014) nor does it automatically carry medical liability for the doctor. Quite the opposite, sometimes are *leges artis* themselves to impose off-label prescription, as it is the case when there is no drug specifically approved for that situation or, though there is an approved drug, it does not work successfully regarding a given patient. Therefore, if in those scenarios the doctor does not resort to off-label prescription he may be violating medical legis artis and he may be held liable (De Nayer, et al., 2013). Confirming this idea is the fact that the English Medical Council (2013) has explicitly allowed off-label prescription, although demanding certain requisites. In sum, off-label prescription frequently corresponds to the best medical standard of care.

In spite of the imposition of mandatory MA stipulated by the European Union (EU) law, the fact is that there is no European rule forbidding off-label prescription or forcing the member States to forbid it.

Furthermore, off-label prescription can also be grounded on the principle of freedom of prescription, which is nuclear to the medical profession, meaning that the doctor can freely choose which drug to prescribe, without being bound by the existence and content of a MA. Indeed, whereas the preparation, promotion and marketing of a drug are strictly regulated, drug prescription falls on the physician's free evaluation, provided it complies with the patient's well-being.

However, when prescribing off-label the risk of medical malpractice increases (Francisco, 2013; Lenk & Duttge, 2014; L'Ecluse et al., 2013; Plate, 2009; Raposo, 2013). Although litigation is not a necessary consequence of off-label prescription, this practice involves more risks in terms of patient's safety and, consequently, imposes a higher set of obligations to be complied with by the doctor. Thus, complaints and lawsuits became far more frequent when the doctor is prescribing off-label, with the aggravating circumstance that insurance policies for professional medical liability rarely cover damages resulting from off-label prescription; therefore, in case of a conviction chances are that the doctor alone will bear the payment of the compensation.

The problem is intensified by the lack of a clear legal definition of off-label prescription, and by the absence of defined requites for lawful off-label prescription. All these omissions turn the exact legal contours of this practice quite blurred. Therefore, it is imperative to create a law establishing the legal framework for off-label prescription in every legal order, i.e., the requirements to be complied by doctors and the rights that patients have in an off-label scenario.

Requisites to be complied by the prescribing doctors

Off-label prescription is commonly considered a risky medical practice. It's a fact that studies present different conclusions regarding the risk of adverse events in off-label uses (FDA, 2014; Obermann, 2013; Pretorius et al., 2013; Velo & Minuz, 2009). Nonetheless, it is undeniable that a drug not specifically tested for a certain use carries a higher percentage of adverse reactions than the one submitted to proper research and clinical trials; thus, it endangers patient's safety (Gillick, 2009; Repucci, 2011). Of course that not all off-label uses involve adverse reactions, but surely this circumstance increases the likelihood of their occurrence (Walton, et al., 2008).
For this reason physicians should comply with certain requisites while prescribing off-label in order to respect medical leges artis and, therefore, to avoid lawsuits (AMA, nd; Barrios Flores, 2014; GMS, 2013; L'Ecluse, Longeval & T'Syen, 2013; Medicines and Healthcare Products Regulatory Agency, 2009; Obermann, 2013; Raposo, 2014; Riley & Basilius, 2007). Some of the requirements are already established by law in the legal orders that created a regulation for off-label prescription, while others simply result from professional guidelines and common sense.

First, doctors should only prescribe off-label if there is no therapeutic alternative duly authorised (Dresser & Frader, 2009). The reason is that if the drug was not submitted to proper clinical trials for that specific medical use its guarantees of safety and effectiveness are much lower comparing with drugs properly tested and approved.

However, this requirement encompasses some exceptions. One of them is still based in medical considerations: suppose that the patient has developed an intolerance to the approved drug due to his/her particular genetic conditions; in this case off-label prescription will be allowed. The other exception is much more debatable, but it is being applied in many countries due to financial concerns: off-label prescriptions based on cost-saving consideration, in order to reduce drug's expenditure, especially when there is a huge price difference between the (more expensive) authorised drug and the (cheaper) off-label alternative.

In addition, the off-label use in question must have solid scientific grounds, for instance, because it has been approved by several scientific studies or because it corresponds to a practice already settled among health professionals.

Following the previous requirement, off-label prescription must be aimed to the patient's well-being; in other words, it has to correspond to the patient's best interest instead of financial purposes. Nonetheless, the correct interpretation of this requisite may be tricky, since when the treatment is paid by the patient himself and the on-label drug is not affordable, the off-label option may be the one that satisfies the patent's interests, since the alternative would be to have no treatment at all.

But in any case the patient must be informed that it is an off-label drug use and provide his consent (European Commission, 2013). In the US the rule of informed consent is not applicable in this regard, since courts tend to consider that medical freedom of prescription also includes the decision to use a drug off-label and that this information is not relevant to the patient. Conversely, in Europe the patient is required to consent regarding off-label drug uses and most of the existing litigation regarding off-label prescription concerns the lack of informed consent.

Another decisive requisite for lawful off-label prescription is the existence of a previous medical evaluation of the patient's condition. Therefore, it is imperative that the decision is taken by the attending physician himself and not by any other decision maker; namely, it cannot be taken by the hospital administration or by the government. This requirement is being growingly waived and off-label decisions are nowadays being currently taken at a higher level. In fact, based on budget constrictions, many governments are encouraging, or even imposing, the off-label use of cheaper drugs, even thought there is a fully approved therapeutic alternative (the Avastin-Lucentis case is paradigmatic in this regards). So, some hospitals belonging to the National Health Care System are not even purchasing the most expensive drug, "forcing" doctors to prescribe off-label. But since in this case the decision is not freely taken by doctors – as it should be – they cannot be held liable for any injury suffered by the patient due to the off-label use. Therefore, the only option is to sue the government for bad management of health resources and for putting public health in risk.

Finally, the doctor is obviously required to comply with the usual rules of the medical profession, but in more demanding terms. Thus, because off-label prescription is considered a risky treatment, the doctor is required to input all information related with the off-label drug use on the patient's medical record and to proceed to the patient's follow up in particularly strict terms.

The scope of medical freedom of prescription

Freedom of prescription is a defining note of the medical profession; therefore, the doctor has the power to choose which drug to prescribe and how to use it, even disregarding the content of the MA, provided he complies with medical leges artis. However, the scope of freedom of prescription has different understandings in the US and in Europe.

In the US this principle is accepted in very wide terms and the competent agency to monitor the production and marketing of drugs - the Food and Drugs Administration (FDA) - does not intrude in any way in drug's prescription (Fairbairn, et al., 2011; Tiwary, 2003). The FDA itself affirmed this position in various statements, declaring that the physician can use a product for an indication not included in the approved label, without the FDA's authorization or notification (FDA, 1982; FDA, 2011; FDA, 2014), and even without informing the patient's that it is an off-label prescription, which is nothing but surprising having in mind the relevance of the patient's informed consent in the US legal order.

Differently, in Europe it is assumed that although the doctor can freely choose which medicine to prescribe, he must inform the patient of all relevant circumstances surrounding the prescription, such as the fact that the drug is being used off-label.

The requirement of solid scientific justification

One of the main requisites for a save off-label prescription is the existence of sound scientific grounds. The doctor has to clarify why he decided to prescribe off-label and justify his decision in proper scientific evidences regarding the safety and efficiency of the off-label use.

Within off-label prescriptions the imposition of sound scientific grounds is especially stringent due to the fact that the drug is being used – at least theoretically – in riskier terms. In spite of it, according with several studies around 70% of all off-label prescriptions lack strong scientific ground (Eguale et al., 2012).

When the off-label use comes recommended by reliable academic research or when it constitutes a common practice already settled on the medical community, these facts suggest that it corresponds to the best standard of care (thought this is a rebuttable presumption)

Of course that this requirement cannot be accepted as rigorously where there is no approved drug for that specific situation, because the alternative would be not to treat the patient at all. Nonetheless, and even in the absence of a properly approved drug for that condition, the existence of data suggesting the likelihood of adverse events should strongly discourage the doctor from prescribing off-label.

The difficulty in satisfying this requisite lays in the absence of reliable scientific information regarding off-label uses. First of all, because pharmaceutical companies are forbidden of promoting off-label uses and the fact is that it does not come easy to distinguish the boundary between promotional activities and merely information

disclosure, so, some informational activities ended up being forbidden. But, and on the other hand, if pharmaceuticals were free to disseminate information on off-label uses, chances are that the data released were "shaped" in order to increase sales. The question is that scientific articles in peer-review journals are not exempted from suspicion in this regard, not only because those studies usually do not encompass a sufficiently wide range of studies and randomised trials; but especially because some of them are actually funded by pharmaceutical companies themselves, to increase off-label uses of their drugs and, thus, to increase the overall sales. In sum, pharmaceutical companies are not unbiased when disclosing information and even supposable neutral experts hired by them are not so neutral in the end (Rodwin, 2013; Steinman et al., 2006).

Informed consent

A crucial requisite of off-label prescription is informed consent (Stafford, 2008, Wilkes & Johns, 2008), required in every medical act but here taken in especially demanding terms. First of all, regarding the formalities to be respected, since it must be a written consent (European Commission, 2012). Furthermore, in what concerns the amount of information to be communicated to the patient. This information should clearly explain that it is an off-label drug use, expose the reasons for that medical option, refer possible negative outcomes that can derive therefrom and also the potential beneficial results expected, discuss other available alternatives (Weynants & Schoonderbeek, 2010) and mention that the respective cost may not be supported by the National Health Service or by the patient's private health insurance (Ask, 2014; Lenk & Duttge, 2014). For instance, a Swiss patient was treated off-label with aesthetic polylactic acid, which was not part of the list of reimbursable medicines, and after a long litigation the health insurance company has won the case on the Swiss Federal Tribunal (Tribunal Fédéral K 147/06).

Actually, most of the European decisions convicting doctors for off-label uses were based on the violation of informed consent rules.

For instance, in 1996 the the highest German court, the Bundesgerichtshof, stated: "The patient must be informed about the use of a non-approved medication, because, whatever the actual quality or safety of the medication, it lacks the sanction of official approval, which may be essential for an individual patient's decision under the scope of the Medical Preperations Act" (BGH NStZ 1996, 34).

In a decision from 2008 the French Cour de Cassation criminally convicted the doctor that prescribed off-label a vasodilator drug (papaverine) to treat the patient's erectile dysfunction, but without informing him about the off-label nature of the treatment. Due to the drug the patient initially suffered a prolonged erection for more than 48 hours, which was followed by a complete and irreversible organic impotence. The Court did not consider that this off-label drug use violated, *de per se*, medical leges artis, especially since it was a treatment that had already presented good results in erectile dysfunction cases, even if it also had some known complications. However, since the off-label nature of the prescription and the risks possibly involved were not communicated to the patient, the doctor turned out to be convicted for the violation of informed consent (Cass. 1re civ., 18 sept. 2008, n° 07-15427).

In 2008 the Italian Corte di Cassazione upheld a doctor's conviction due to an off-label prescription (Corte di Cassazione Penale sez. IV 24/6/2008 n. 37077). The doctor had prescribed Topamax (topiramate), which is authorized to treat epilepsy, but that in the case was used to treat an obesity problem. The problem arose because neither the doctor explored other alternative treatments nor reported that this was an off-label drug use. Moreover, the doctor also failed in the patient's follow-up during the treatment and in addition refused to change the drug's dosage despite the fact that the patient was showing negative effects. But according with the Corte the most serious misconduct was the lack of informed consent (in the case from the patient and/or is parents – depending on the legal order – since the patient was a minor). The Court noted that, although off-label prescription is a lawful practice in light of the Italian law (Law Decree n. 23, from 17/02/1998), it is of crucial importance to provide the patient with complete information, including the possible adverse effects and contraindications of the therapy used, as follows from Article 32 of the Italian Constitution (Cass. 1re civ., 12 juin 2012, n° 11-18327).

In 2012, still the French Cour de Cassation ruled in his same sense. The case regarded a rheumatologist doctor who had administered an intradiscal injection, Hexatrione®, to relieve back pain. The treatment failed and the patient started to show calcifications, thus he filed a lawsuit against the doctor, arguing that if he had known that the prescription was off-label he would have refuse the treatment. The Cour de Cassation concluded that the doctor violated the standard of care, by not informing the patient about the off-label character of the treatment and about the consequent risks (although this was a frequent treatment and without known risks). Thus, the patient was entitled to compensation.

Manufacturer's liability

Off-label promotion – that is, the advertisement of drug uses that are not included in the MA - is an unlawful practice in Europe (and actually in most legal orders), even if the patient's does not suffer any injury. So, this practice will carry a financial penalty for the pharmaceutical company, which may be a very large sum. This responsibility comes as consequence of the violation of the rule prohibiting off-label prescription.

Furthermore, the manufacturer may be held liable for the patient's injuries, in alternative or cumulatively with the doctor's liability. The pharmaceutical company will take the responsibility for injuries suffered by the patient if it promoted the off-label use or, even if there was no promotion, if the company was aware of the off-label use and in spite of it did not take any measure to prevent that use.

Therefore, many companies feel compelled to discourage off-label prescriptions, especially by including in the drug's leaflet the proper drug use and all the contraindications of the improper use, in order to be protected from eventual liabilities derived from the lack of information to the consumer (Abbott & Ayres, 2014).

Some companies even took active measures to prevent off-label uses of their drugs. For instance, in the aftermath of recent events related with the reimbursement of Avastin to treat ADM in some European countries, the pharmaceutical Roche – the manufacturer of Avastin - said in a statement to Bloomberg: "In general, Roche supports the overall approach that physicians should have the freedom to prescribe the

medicine they think is right for their patients" (…) "At the same time, it is our obligation to inform the medical community including physicians and patients about the known risks associated with the off-label uses of our medicines".[1]

However, if the producer was totally oblivious to the off-label use of its products – i.e., he took all reasonable measure in order to prevent that use or he was not even aware of it – the producer won't be held liable for any injury suffered during the off-label use.

Conclusions

Off-label prescription is a medical practice that is not going to stop in the near future' Quite the opposite, is being encourage by the astonishing speed of scientific developments, that always run faster than the bureaucracies of the demanding process of drug's approval.

Actually, it is not even desirable that it stops, since all players in the health care sector are interested in the maintenance of off-label prescription: patients want it because frequently this is the only mechanism to have access to medicines likely to produce some kind of beneficial effect on them; doctors want it since off-label prescription may be the only alternative to treat some patients, instead of leaving them without any kind of treatment, thus, off-label prescription frequently allows the doctor to comply with the best standard of care; pharmaceutical companies also want it because off-label uses became an easy source of profit without much investment: governments want it since the off-label use of cheaper drugs is becoming a solution to cut expenses in the health care sector;

However, the danger is that these stakeholders get so seduced by the potential benefits that they end up disregarding the basic requirements that should guide every drug prescription, namely the patient's well-being.

Ultimately, the decisive aim of the doctor must be to act in the patient's best interest instead of guided by commercial or economic reasons; and the patient's best interest demands a therapeutic grounded in proper scientific basis. In other words, it is not because a certain medicine is cheaper that doctors must prescribe it (on-label or off-label), but because evidence based medicine and reliable scientific data justify the use of the drug in those conditions.

[1] http://www.bloomberg.com/news/articles/2014-06-10/italy-to-fund-unapproved-use-of-roche-drug-to-cut-costs

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