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***International
Journal of Health &
Life Sciences***

[ISSN: 2383-4390] [eISSN: 2383-4382]

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DOI: <http://dx.doi.org/10.22110/IJHLS.2017.80512>

Classification: Health Economics

You can cite this article as follows:

Raposo V. L. Is money thicker than health? - Economic motivated off-label prescription in an austere Europe. *Int J Health Life Sci.* 2017, 3 (1): 44-59.



Is money thicker than health? - Economic motivated off-label prescription in an austere Europe

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ARTICLE INFO

Article Type:

Review article

Article History:

Received: 2017-06-02

Accepted: 2017-06-15

ePublished: 2017-07-01

Keywords:

Legislation & jurisprudence

Legislation

Drug

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ABSTRACT

Off-label prescription is common in Europe and economically motivated off-label prescription is being increasingly recognised by the national laws of the Member States of the European Union, even though both European law and the European courts refute the prevalence of financial considerations over public health.

This article examines the causes of economically motivated off-label prescription, the current legislative and administrative measures implemented in several European countries and its consequences, and it concludes that in very specific scenarios off-label prescription grounded in economic reasons should be allowed.

Introduction

Europe is experiencing a period of austerity [1-2]. Due to increases in health care expenditures (also because of an aged population [3]) that have largely surpassed economic growth [4], the health care sector is not excluded from cost-cutting strategies. Measures such as reductions of health care staff and the diminution of working hours are becoming widespread in Europe. Drugs are one of the domains more particularly envisaged by this economists' approach, because it is well-known that drug prices – especially in the case of new drugs – are sometimes prohibitive and do not always conform with their added benefits. Therefore, national health services (NHSs) and private insurers are opting for generic drugs instead of brand-name drugs and for off-label prescription of cheaper drugs instead of specifically authorised drug uses.

However, the decision to resort to off-label prescription for exclusively economic reasons raises many issues, both from a legal standpoint and from a patient safety approach, even if grounded in the intention to ration the scarce

resources of an NHS.

The solution for this dilemma lays in finding the best method to achieve both of these goals – to increase savings in health care delivery and to increase patient safety – or, as an alternative, to evaluate which should prevail. We must also consider other issues, such as the level of investment in health innovation and the protection that should be granted to intellectual property rights. Taking all of these elements into consideration, this paper will argue that economic considerations and rationing of health care resources has become not only acceptable, but even necessary in times of austerity. Of course, in a perfect world, every citizen would have guaranteed access to optimal health care. In a less-perfect world, but in an economically stable environment, it is possible to successfully pursue the goal of providing optimal health care to everyone. In a scenario of economic austerity, however, in which cuts in health care costs are inevitable, the lesser evil is to cut those with a cheaper option, instead of cutting the ones for which no alternative exists. This paper begins with an explanation of off-label drug prescription

and the reasons for this practice, including the financial considerations that explain why pharmaceutical companies do to not require a MA to certain drug's uses. The aim of that first part is to demonstrate how money and profit condition the marketing decisions of pharmaceutical companies. It should be noted that the paper does not deal with off-label prescription decided by the prescribing doctor for a particular situation and for a specific patient, based in sound scientific grounds and having in consideration the patient's best interest, a practice deemed to comply with medical *leges artis* and to correspond to the best standard of care [5]. Conversely, the paper intends to discuss the cases in which the off-label use is purely grounded in financial reasons, as a mechanism to cut health care costs. For this purpose the paper describes the Avastin/Lucentis dilemma as a case study aimed to demonstrate the specific problem that will be analysed. Then it examines some of the latest financially motivated health care policies within the Member States of the European Union (EU), pointing out how European governments (not doctors) are encouraging off-label drug uses as a solution to decrease health expenditures (not to promote the patient's well-being), and underlying the possible conflict between these policies and EU law. Finally, the paper considers the implications of economic off-label prescription in light of public health and patient safety. After these considerations, the paper concludes not by condemning all off-label prescription based on economic reasons, but instead by accepting it in very specific scenarios. Some other measures can be envisaged to this same purpose, such as compulsory licencing and even a reformulation of the entire drug's approval mechanism. However, this paper is not focused on those other alternatives.

I. Definition of off-label prescription

After some tragic incidents caused by the ingestion of untested drugs, the production and marketing of drugs became highly regulated and submitted to strict control from specialised agencies: the European Medicines Agency (EMA)

in Europe, the Food and Drug Administration (FDA) in the United States, and the China Food and Drug Administration (CFDA) in China. Accordingly, before a drug is released into the market, the pharmaceutical company is required to submit to the competent agency an immense set of studies and clinical trials to prove that the drug is effective and does not involve excessive risk for the consumer. In the end, the objective is to obtain a Marketing Authorisation (henceforth MA), which basically operates as a warrantee seal regarding the drug's efficacy and safety [6-9]. The MA does not provide this guarantee in general terms (actually, not even in specific terms, because drugs are such risky products that there is no way to ensure their safety, even if submitted to the entire approval process), but only for the specific uses that fall within the scope of the MA – that is, for the exact patients, the particular diseases, the correct dosages and the precise methods of administration – and that are also described in the Summary of Product Characteristics (SmPC). However, it is not unusual for a drug to be prescribed outside the terms of its MA, a practice known as off-label prescription. In this scenario, the drug is prescribed for a group of patients, a medical condition, a dosage or a posology that is not stated on the MA. It can be quite complex to identify an off-label prescription, largely because the exact contours of this reality are still blurred, and in many legal orders we cannot rely upon its legal definition. As regards European law, there is no proper definition of this practice concerning medicines for human use, but only in Directive 2001/82/EC regarding veterinary uses [10]. Matters are even more complex because many different practices may fall under the classification of off-label prescription, from minor adjustments in the duly approved use to radical modifications, including drug manipulation and reformulation. When the deviation from the authorised drug use is hardly relevant, it may be questioned whether that use can still be covered by the existing MA, which, in turn, depends on the specificity of the MA's terms. In contrast, if the modification implies reformulation of the drug, the question is to determine whether it is still in the domain of an

off-label use or, conversely, if we are facing the creation of a new drug.

II. Reasons for off-label prescription

In an ideal world, all drugs prescribed would be specifically authorised for that particular use. Every single drug would be subjected to a vast array of tests and clinical trials and to a scrupulous process of analysis regarding both its risks and its benefits. In the case of a positive appraisal, an MA would be granted and the drug could then be used only within the terms of that MA. However, many different factors may lead to a different scenario. For instance, an MA for a specific use may have been denied due to a lack of scientific evidence [11]. Indeed, the current regulatory system presents a very high rate of MA refusal. According to a study that analysed the EMA's activity between 2003 and 2010, 70 MA applications were withdrawn by the applicant and 16 were denied, making a total of 86 unsuccessful applications due to lack of quality, safety and efficacy [12]. This outcome may be criticised because the potentially excessive level of demand from the approval authorities threatens public health by depriving patients from using safe drugs. However, it also operates as a powerful filter for dangerous products. In effect, sad episodes involving non-scrutinised drugs – see the infamous Thalidomide scandal – forced drug authorities to prefer prudence to speed in the granting of MAs. Another possible scenario relates to cases in which an MA for a specific use is indeed required and is in the process of approval; in the meantime, its use for that purpose is considered necessary, therefore leading to a temporary off-label prescription. In some other situations – actually, the most frequent ones – an MA is not even required. In fact, for reasons related to commercial strategies, pharmaceutical companies sometimes do not request an MA for all potential uses of the drug, even though those other uses may be well known at the time the MA is requested. (In some other cases, they are identified later.) When that happens, regardless of the benefits that the drug may carry for potential patients, the MA cannot be granted *ex officio* without a request from the MA holder. In fact, governments, regulatory entities and patient

groups cannot request an MA or even argue relevant public health reasons. Nonetheless, even though a drug is not specifically approved for a given use, it may be known in the medical community that it can be applied for that use, that is, with another dosage, frequency or posology, for a different group of patients or for a different medical condition [13]. The fact that the drug was not specifically tested for these other uses does not immediately preclude its efficacy and safety. The pharmaceutical company's strategy of not requesting an MA for a particular use is usually grounded in reasons related to risk management, from either a legal or an economic perspective. In effect, each MA request involves a huge panoply of clinical trials and additional research, rendering the entire procedure very long and costly. Therefore, pharmaceutical companies will only enlarge the scope of the existing MA request or require another MA when it is reasonable to expect a significant profit without much risk of loss or litigation. It should be noted that the development of a new drug is an extremely expensive task (an assessment made by a worldwide expert in economy and health estimated that the total cost to develop and obtain marketing approval for a new drug is about \$2.6 billion), so, ultimately, this evaluation is grounded in economic reasons [14-15]. Even the aim of avoiding lawsuits is still connected with the need to limit financial losses derived from court compensations, reputation damage and consequent sales decreases. In contrast, off-label uses can actually increase sales (and thus profits) while sparing the company all of the investment involved in an MA request [16]. Thus, many companies maintain and encourage off-label prescription, even though off-label promotion is generally forbidden and heavily punished [17-18]. A detailed overview of the reasons that pharmaceutical companies may not be willing to request an MA helps to explain off-label prescription and its underlying economic motivations – from the drug's manufacturer, from the prescriber and from governments.

A. Risky Clinical Trials

Pharmaceutical companies want to avoid MA procedures that involve risky clinical trials, that is,

clinical trials that demand more investment and time and, especially, that can trigger lawsuits. This is particularly the case for clinical trials involving the elderly, pregnant women or children. Each is a vulnerable population for whom the risk of suffering an injury during the clinical trial is much higher and – *et pour cause* – the legal impositions are also more demanding, especially in terms of safety guarantees. In addition, they require specialised technicians and possibly particular medical devices to conduct these clinical trials. Furthermore, the trials take longer because it is not easy to find suitable participants to cover all possible hypotheses (for instance, children in each age group or pregnant women with different ages, medical conditions and pregnancy stages). For these reasons, pharmaceutical companies avoid organising clinical trials with these participants. Thus, MAs for drugs to be used in these patients are rarely requested, which makes off-label prescription particularly frequent in paediatric ^[19-20], geriatric ^[21] and obstetric ^[22] medicine.

B. Unprofitable Drug Uses

The risks involved in launching a drug into the market can be very stringent; therefore, only in the presence of a high cost-benefit ratio will the manufacturer invest in an MA request. At the opposite end of the scale, an MA will not be requested if the expected benefits are not sufficiently attractive, either because the number of potential consumers is too low or because the new use would compete with drugs that are already established in the market. The first scenario – a reduced number of consumers – is especially frequent in the context of rare diseases, known in European law as ‘orphan diseases’, which are chronic debilitating diseases or life-threatening conditions that affect a very small number of people in the entire world, as defined in Regulation (EC) 141/2000. Therefore, there is no expectation of a large number of sales, which makes investment in those uses very unattractive and leads to the exponential growth of off-label prescription in the domain of orphan diseases. To remedy the lack of authorised medicines for orphan diseases – the so-called orphan drugs – European legislators have created legal

mechanisms to encourage pharmaceutical companies to invest more in orphan drugs (or in orphan uses of non-orphan drugs), such as Regulation (EC) 141/2000 and the implementation of the Committee for Orphan Medicinal Products within the EMA.

III. Economic considerations in off-label prescription

A. Drugs Are Not Free

Some drugs have such an exorbitant price that they became a huge burden for payers ^[23] (i.e., an NHS, private medical insurance schemes or even the paying patients themselves), which forces them to look for cheaper alternatives to reduce the financial burden, even if the substitute drug has not been specifically authorised for that medical condition. The dilemma becomes particularly stringent whenever the cheaper drug that is being used off-label is substituting for a duly approved drug (the paradigmatic example of this scenario is the case of Lucentis and Avastin, to which we will refer later in this study), because in this scenario the patient could indeed have access to an authorised drug for his particular condition, but he or she ends up being deprived of that drug because of monetary considerations. One might think that the solution for this problem would be to obtain approval for uses that are currently considered off-label. However, chances are that after the approval, the formerly less-expensive drug would adopt the price of the already-authorised drug, thus overturning the benefits expected with this move. A note that should be underlined regarding economic savings from using a less-expensive drug is that traditionally off-label uses are not covered by the NHS or by private insurance schemes; therefore, the apparent savings may eventually become a cost for the patient. However, the situation was recently reversed, and in some legal orders the NHS is now covering selected off-label uses for the purpose of cutting health care expenses. The fact is that many governments are currently issuing legislation aimed to provide a legal basis for the off-label prescription of cheaper drugs and to

guarantee their reimbursement. Those events gained the attention of the European Parliament, which, in a Resolution from 22 October 2013 (even before the surprising legal developments in France and Italy) asked the EMA to prepare a list of medicines that were being used off-label despite of the existence of approved alternatives and to issue guidelines for off-label uses ^[24].

B. Drugs Reimbursement

The evaluation of the judicial framework of off-label prescription demands two different considerations: first, to determine whether the law forbids it, authorises it or even imposes it; and second, if it is concluded that this is a legitimate practice, to determine whether off-label drug uses are reimbursed by the respective NHS or by private health insurers. Reimbursement is regulated by European law (namely Directive 899/105 ^[25]), but in a way that leaves complete freedom to Member States regarding the decision about which drugs can be reimbursed and how. There is not even an express prohibition regarding reimbursement of medicines prescribed off-label. However, reimbursement under these conditions cannot annihilate the system of drug authorisation, as stipulated by European law. The decision about which drugs receive reimbursement takes into account the drug's respective therapeutic value and clinical benefits compared to those of other products; these two elements of evaluation are largely dictated by safety and efficiency criteria. However, in the case of off-label uses, those data are unknown, not only because not all of the information is available from studies and clinical trials performed for authorised medicinal products, but also because most of the time, records regarding off-label prescriptions, let alone their adverse effects, are not kept ^[26]. Given the almost total lack of data, it is understandable that national authorities are traditionally unwilling to reimburse for a drug under these conditions. Nevertheless, this difficulty does not mean that the reimbursement of off-label prescriptions is impossible. Reimbursement is still possible in consideration of criteria such as the extent of deviation between the off-label use and the MA's content and the specific needs that require off-label use in the

context of the right to health care. In fact, some countries are already reimbursing off-label prescriptions, mostly on the basis of a cost-benefit assessment. In other words, off-label uses are particularly driven by financial concerns, namely, the thirst for profit that motivates pharmaceutical companies, either for direct profit derived from an increase in sales or indirect profit from the management of potential liabilities that result from riskier clinical trials. In addition to the economic motivations of pharmaceutical companies, there is another reason for off-label uses based on economic considerations: health policies from governments in austerity, which are more focused on expense control than on public health and patient safety ^[27-28].

IV. A Case Study: Avastin and Lucentis

The Avastin/Lucentis case is a good case study to evaluate the predominance of financial motivations in health care delivery, even at the expense of patient safety ^[18]. To understand this case, we must begin with the origin of these two drugs. Both were developed by Genentech, a biotech company in the Roche Group. Lucentis (ranibizumab) was specifically designed to treat eye diseases such as diabetic macular oedema and age-related macular degeneration, and these uses are expressly covered by its MA. In contrast, Avastin (bevacizumab) was created to treat some types of cancer that are not related to any eye condition; therefore, its MA does not cover that type of use. However, the fact is that both Lucentis and Avastin can efficiently treat eye diseases, which led some doctors to prescribe Avastin for eye conditions. It is a fact that different studies came to different conclusions regarding the safety and efficacy of these drugs: some state that Avastin does not carry a higher risk of adverse events ^[29-30], whilst others claim the opposite and underline that although both drugs are equally effective, the possibility of adverse reactions is much higher with Avastin ^[31]. The main motivator for the doctor's choice is financial. In effect, although the prices may vary in different countries, Lucentis is almost 10 times more expensive than Avastin. For instance, in Italy an injection of Lucentis costs 900 euros, while the price of an off-label injection of Avastin is around

81 euros ^[32] and the same price difference is common all around Europe. The price difference is so dramatic that even if Lucentis was more effective than Avastin, this fact might not be enough to establish its use. In an analytical study performed in 2007, when the price of Lucentis was 100 times more than the price of Avastin in the United States, the authors concluded that '[r]anibizumab is not cost effective compared to bevacizumab at current prices unless it is at least 2.5 times more effective. However, in observational studies bevacizumab appears to have similar efficacy' ^[33]. Therefore, it seems that the logical decision is to prescribe Avastin. The problem with this apparently rational choice concerns patient safety. Indeed, the mere fact that Avastin was not specifically tested for eye diseases raises doubts about its efficiency and safety, because it was not submitted to clinical trials to treat those medical conditions. Nonetheless, even if Avastin were as safe as Lucentis for the treatment of eye conditions, the fact that it requires manipulation creates a new source of risk. In effect, Lucentis is commercialised specifically for intravitreal injection; thus, it is packaged in very small portions, as required for that use. In contrast, the package of Avastin is much larger because the product was conceived for other purposes; therefore, it is always necessary to divide it into smaller portions, adequate for eye injections – in other words, the drug must be manipulated. The problem is that manipulation is a dangerous practice, not only because it increases the risk of contamination, but also because of the risk of confusing containers, and thus of applying the wrong product, as is suspected to have occurred in the so-called Portuguese scandal of 'cegos do Hospital de Santa Maria' (St. Mary's Hospital blind people). This case was allegedly caused by confusion between one bottle that contained Avastin after it was divided into smaller doses and another bottle with another substance. In the end, the mistake led to the application of the wrong product in the eyes of six patients, leaving them irreversibly blind, either totally or partially ^[34]. In awareness that litigation may increase with the off-label use of Avastin, Roche rushed to disclose a communication

alerting physicians to the potential risks involved in the off-label prescription of its drug ^[35]. However, the fact is that bevacizumab is currently included on the World Health Organisation's list of essential medicines (WHO 2015) in the section of anti-vascular endothelial growth factor preparations, which leads to the conclusion that economic considerations are taking the lead ^[36].

V. European countries move towards cutting costs in drug use

Off-label drug uses are quite often cheaper than the drug especially authorised for that same use. For this reason, many governments are currently issuing legislation aimed to provide a legal basis for the off-label prescription of cheaper drugs. The first European country to follow this path was Italy ^[29]. Off-label prescription had long been expressly recognised by law in Italy. Law n. 648/1996 ^[37] ascertains that a medicine can be used off-label if certain requisites are fulfilled, namely, if no valid therapeutic alternative exists. Under this regime, the off-label use can be reimbursed by the NHS, and for that purpose the Italian pharmaceutical agency (Agenzia Italiana del Farmaco) holds a periodically updated list of all drugs that allow reimbursement, the so-called 'List 648'. Later, Law n. 94/1998 allowed doctors, on their own accountability, to prescribe off-label, under the compliance of some other requisites, although the drug's use would not be reimbursed. In 2014, due to Law Decree 36/2014 ^[38], the off-label prescription of cheaper drugs was legally encouraged, as this regulation came to admit the inclusion of off-label drug uses in List 648, thus allowing their reimbursement. This is now possible even in the presence of a specifically authorised drug for the same use, as long as some other requisites are filled: a cost-effectiveness evaluation, recognition of that off-label use by the scientific community and conformity with the scientific research developed in the field. In sum, the reimbursement for off-label uses became mostly dependent on cost-effectiveness considerations. The final result was the reimbursement of Avastin instead of Lucentis to treat age-related macular degeneration. This legal

option generated much controversy, and at some point the Italian Constitutional Court was called to intervene; it decided that the Italian pharmaceutical agency could include on List 648 products that are used off-label to substitute for authorised drugs ^[39]. However, some years before, the Italian Constitutional Court took a different approach regarding off-label drug use, even though the surrounding events were different. In 2011, the Court declared the illegality of a norm belonging to a regional law (Legge della Regione Emilia-Romagna, n. 24, from 22 December 2009) that authorised the prescription of unapproved drugs that present the same degree of safety and efficacy recognised to licensed drugs to reduce drug expenditures ^[40]. The Constitutional Court condemned the practice because it considered that the regional executive was usurping functions that legally fit the state authority, the one responsible for checking the safety and efficacy of medicines. The constitutional jurisdiction also stressed that allowing regional administrations to freely decide which drugs could be prescribed in their respective hospitals would create deep inequalities between the inhabitants of the various parts of the country. In fact, individuals who had the misfortune to live in an area that would allow the use of drugs that were not specifically authorised would clearly be at a disadvantage compared to those whose regional administration strictly complied with the competent pharmaceutical authorities. Nonetheless, this argument lost its value, because this measure is not currently being adopted by a single region, but by the entire Italian territory. A similar situation occurred in France ^[29, 41]. In 2011, Act n. 2011-2012, from 29 December 2011, which reinforced the safety of medicines and health products, was issued to regulate off-label uses ^[42]. The act modified several norms of the Public Health Code (Code de la Santé Public, hereafter CSP) to provide legal grounds for off-label prescription, always under the physician's responsibility and so long as he or she acts according to the patient's best interest. Thus, physicians can freely choose the treatment they consider to be most suitable for the particular patient's condition, according to the existing legal framework and known scientific data, to 'ensure a high quality, safe and effective treatment' (Article

R.4127-8 of CSP). In effect, doctors can prescribe drugs that do not have an MA in compliance with two distinct figures: the Temporary Authorisation for Use (TAU) and the Temporary Recommendation of Use (TRU). The TAU is issued by the French National Security Agency for Medicines and Health Products (Agence Nationale de Sécurité du Médicament et des Produits de Santé – ANSM) and is intended to provide a legal framework for the use of new treatments, not yet authorised, in case a risk-benefit assessment endorses that use. The TRU is also issued by the ANSM after a risk-benefit evaluation, but for drugs that have already been authorised in the French market regarding uses that are not covered by that authorisation (Article L5121-12 and R5121-76-1 CSP) ^[42,43]. The configuration of the TRU has changed over the years. Initially, the TRU was intended to allow off-label prescription in particular scenarios – costly and innovative drugs, rare conditions or long-lasting diseases – and as long as the ANSM confirmed the existence of strong scientific justifications. In any case, off-label prescription was not allowed if another drug had been expressly authorised for that same purpose. However, when French authorities realised that this practice could carry huge savings for the NHS, several TRUs began to be issued for cost-saving purposes, even when an authorised therapeutic alternative existed (Degrassat-Théas et al. 2015). In fact, in 2013 there was an attempt to create a kind of TRU based on economic considerations, intended to cut expenses in health insurance finances. However, this measure did not enter into force, namely due to the ECJ ruling in the case *Commission v. Poland*; the French lawmaker was thus forced to mitigate this intention by deleting the express economic references. Even so, the CSP eventually came to allow TRUs to be granted even when an approved drug is available for that treatment. Following this path, in 2015 a TRU was granted to bevacizumab, disregarding Roche's opposition, thus leading to a judicial conflict between Roche and the French government. In the United Kingdom, off-label prescription is allowed under the Medicines Act and Regulations 1968, but with some requirements and under the control of the NHS (2013). The General Medical Council and the National Institute for Health and Care

Excellence (NICE) also issued a number of recommendations in this regard, which are usually followed by doctors, in particular stressing the need for the doctor to conclude that the off-label use serves more suitably the patient's needs than the use of a duly authorised product ^[45]. An Unlicensed Medicines Request Form was established with which the physician may apply for off-label uses; in addition, the Unlicensed Medicines database was created, which lists the already-approved off-label uses and the risks detected with those uses. The reimbursement of off-label uses within the NHS is decided by Clinical Commissioning Groups (CCGs), some of which control their own budgets. In addition to this general funding procedure, there is also the possibility of obtaining funding by means of an NHS Individual Funding Request presented by the prescribing physician. The NHS took a step further and is also allowing off-label reimbursements on the basis of financial considerations. In addition, the NICE is now considering non-approved drugs – that is, not approved for that specific use – for cost-benefit evaluations to make recommendations to the NHS ^[46]. In particular, the NICE has included Avastin – that is, its off-label use – in the cost-effectiveness assessment for the treatment of age-related macular degeneration. In 2014, the Off-Patent Drugs Bill aimed to provide a legal basis for new indication regarding drug uses that are currently off-label, but that can be very useful for patients, with the aim of forcing the British government to obtain MAs for those uses. The main scope is clearly off-label uses that are much cheaper than the on-label uses. The final purpose is to reduce off-label uses in the United Kingdom and to decrease the NHS's costs. However, the bill did not receive enough public support, and although its initial version was improved, it is still under discussion. In Germany courts not only allow certain off-label prescriptions, some even impose this therapeutic option in cases involving the patient's well-being ^[29]. For instance, in the early 1990s, a Cologne court stated that a doctor was required to issue an off-label prescription for serious illnesses (Oberlandesgericht Köln, decision from 30 May 1990 27 U 169/87). As for reimbursement ^[47-48],

the basic rule is that reimbursement for off-label uses is not allowed under the SGB V (Sozialgesetzbuch). Nonetheless, in 2002 the Federal Social Court (BSG) approved the reimbursement of off-label uses by the German NHS, provided that no other therapy was available for that condition and that credible scientific data on the success of that treatment were available (B 1 KR 37/00 R, decision from 19 March 2002). After this ruling, four expert panels were established with the purpose of defining which off-label uses could be reimbursed. A few years later, in 2005, the German Constitutional Court (BVG) made more flexible the requirements established by the BSG for off-label prescription because they were considered to be hardly achievable in reality. Indeed, the imposition of the existence of scientific data to justify off-label prescriptions was understood by the BSG as requiring that the MA's application had already been submitted by the producer and, in addition, that the results of the respective phase III clinical trials had already been disclosed. What the BVG came to argue was that this understanding violated the German Constitution, namely, the welfare state principle and the state's duty to protect its citizen's life and health. Accordingly, the BVG ruled that in case of serious and life-threatening diseases, the state should cover the costs of off-label treatment, so long as the attending physician concluded that the off-label prescription in question could produce good results in that patient, even though the beneficial effects had not been described in scientific studies (BVerfG 1 BvR 347/98, decision from 6 December 2005 (the so called Nicholas decision)). One year later this new approach was confirmed by the BVG (BSG B 1 KR 7/05 R, decision from 4 April 2006). In the Netherlands, off-label prescription is not forbidden, but the existence of proper protocols and guidelines issued by competent professional entities (article 68 of the Dutch Medicines Act, the *Geneesmiddelenwet* - the full text in Dutch at <http://wetten.overheid.nl/BWBR0021505/2012-01-01>) is required ^[29]. The most important guidelines come from the Medicines Evaluation Board and the Dutch Healthcare Inspectorate. These guidelines distinguish between 'correct off-

label use' and 'incorrect off-label use', and the differentiating criterion relies upon the existence of sound scientific bases (or the lack thereof). If the off-label use has scientific justification and no other therapeutic alternative is available for that patient, the doctor is even expected to prescribe off-label, but in any case, the patient must be informed about the off-label nature of the treatment. The so-called 'correct off-label uses' can be reimbursed. In fact, the Netherlands is moving towards a scenario in which only the off-label use is reimbursed in cases of very expensive treatments. For instance, in regard to treatments for age-related macular degeneration, Avastin is currently in the DBC (diagnose behandelingscombinatie), whilst Lucentis is categorised as an expensive drug. Thus, Avastin is the recommended drug and is used in 80% of cases of age-related macular degeneration.

VI. Off-label prescription from the perspective of European law

Although the EU was not created to deal with health issues, they are currently amongst its main concerns, and Article 168 of the Treaty on the Functioning of the European Union states that 'a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities'. In sum, health promotion is one of the EU's guiding criteria. In the framework of this basilar goal, various European policies are related to health and specifically to drugs made available on the European Market. In this regard, Article 6 of Directive 2001/83/EC [49] states that no medicine should be on the market of a Member State unless it has an MA issued by either the EMA or the national authority in charge. Because the mechanism for a drug's approval is a cornerstone of health care policies, only in exceptional cases can a drug that lacks the mandatory MA be prescribed. Nonetheless, this crucial principle allows for some exceptions for which a drug can be made available even without the proper MA, especially in cases of so-called compassionate use, a practice that allows the disposal of a drug to a particular patient (someone suffering from a serious disease whose health is greatly weakened or who is experiencing a life-threatening

situation), even if it has not received an MA. In any case, exclusions to this principle shall be restricted to exceptional situations, all based on therapeutic considerations. Off-label prescription is also an exception to this principle. It is not forbidden by European law, and it can be argued that Article 5(1) of Directive 2001/83/EC provides legal grounds for this practice. The norm allows Member States to adopt national legislation that excludes from the provisions of the Directive 'medicinal products 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' to 'fulfil special needs'. Although the norm does not refer directly to off-label prescription, it is possible to conclude, by analogy, that European law does not condemn this practice either. Furthermore, Directive 2004/27/EC [50] came to insert in Directive 2001/83 an article 126a, which allows the marketing of products for which approval is still pending, provided that such a decision is justified for public health reasons. Therefore, the kind of off-label prescription foreseen by European law always has therapeutic motivations, not economic ones, because the prevalence of health over economic considerations is a common stand in European law. Therefore, none of the referred exemptions intends to authorise special solutions on the basis of financial stability goals [51]. This is not to say that concerns about savings in health care have no place in European law. For instance, in the *ABPI case* (case C-62/09 *The Queen, on the application of Association of the British Pharmaceutical Industry v. Medicines and Healthcare Products Regulatory Agency* [2010] ECR I-3603), the ECJ allowed national public authorities to grant incentives to doctors to prescribe cheaper drugs instead of more expensive ones, but only if both are equally authorised. Nonetheless, it is worth nothing that this ruling refers only to authorised medicines; it does not mean that Member States can influence therapeutic choices to opt for medicines that do not have an MA for that particular use. Indeed, health promotion presides over all European legal regulations in the pharmaceutical field, as stated in point 2 of Directive 2001/83. Furthermore, European case

law has repeatedly spoken out against the invocation of budgetary reasons by the Member States to escape from compliance with European rules regarding the free movement of goods and services in health care provision. The European Court of Justice (ECJ) stated this basic principle long ago. In fact, in 1996, in *UK v Commission* (case C-180/96 R *UK v Commission (BSE)* [1996] ECR I-3903), the Court recognised the predominance of public health over economic concerns (case C-180/96 R *UK v Commission (BSE)* [1996] ECR I-3903). Later on, in *Artegodan GmbH and others* (joined cases T-74/00, T-76/00, T-83/00, T-84/00, T-85/00, T-132/00, T-137/00 and T-141/00 *Artegodan GmbH and Others* [2002] ECR II-4945), the First Instance Court expressly invoked a 'general principle, identified in the case-law, that protection of public health must unquestionably take precedence over economic considerations'. Soon after, in *R Solvay Pharmaceuticals BV Council of the European Union* (T-392/02 *Solvay Pharmaceuticals BV Council of the European Union* [2003] ECR II-1825), the ECJ stated that 'the requirements of the protection of public health must undoubtedly take precedence over economic considerations'. The most unequivocal statement, however, dates to 2012, in the ECJ decision in *Commission v. Poland* (case C-185/10 *European Commission v Republic of Poland* [2012] ECR I-0000), in which the Court reinforced the condemnation of prescriptions based on economic motivations. Following the opinion issued by the Advocate General in this case, the ECJ upheld the conviction of the Polish government, concluding that Poland had failed to fulfil its obligations under Article 6 of Directive 2001/83/EC. In this case, Poland was allowing drugs with the same active substances, dosage and form as authorised medicinal products already marketed to enter the Polish market whenever those products had a lower price than the authorised drugs (this was not the first of this kind of cases against Poland. In 2010 the ECJ issued a decision regarding the granting of marketing authorisations for several generic medicinal products (case C-385/08 *The European Commission v the Republic of Poland* [2010], ECR I-178), concluding that Poland failed to fulfil its

obligations under Article 6(1) of Directive 2001/83/EC, in conjunction with Article 13(4) of Regulation (EEC) No 2309/93, and Articles 89 and 90 of Regulation (EC) No 726/2004). The ECJ condemned this practice, but the decision left the door open for one specific possibility: the non-authorised use of drugs that do not share the same active substances, dosage and form of the authorised drugs. It is thus possible to conclude that off-label prescription is not against European law when an authorised therapeutic alternative is available, provided that the alternative drug does not have the same active ingredient, dosage and pharmaceutical form as the off-label one ^[41]. However, even if we conclude that off-label prescription is allowed in this scenario, current national regulations face another difficulty, this one related to the person or entity that is entitled to decide upon the off-label use. In effect, according to Article 5(1) of Directive 2001/83/EC, exceptions to the general imposition of a mandatory MA may only be allowed if decided by the prescriber doctor and under his responsibility; clearly, this is not the case whenever off-label drug uses are imposed by administrative measures or by legal norms and are decided by people who never see the patient, as actually occurs in many European countries nowadays. These new trends in health and economy have already eroded the relationships between some governments and the pharmaceutical industry (for instance, a formal complaint against France was presented in the European Commission by the European Federation of Pharmaceutical Industries and Associations, the European Confederation of Pharmaceutical Entrepreneurs and the European Association for Bioindustries) ^[52]. Furthermore, these new policies may also disrupt the relationships between the EU and its member countries. In fact, this kind of measure risks violating European law, not only because it undermines the entire mechanism of drug approval but also, *et pour case*, because it may put patients at higher risk, thus violating one of the basic goals of the modern EU. It can also be discussed if the approved drug is actually the best therapeutic alternative, and in fact some scholars have sustained that drug's approval is not that

decisive in terms of drugs safety and efficiency [53], but this is not the topic of our study. In that light, we now deal with the real world, in which patients are actually dying or suffering severe damage to their health because they are being deprived of effective drugs. The authorised medicine is prohibitively expensive, and neither the health care system nor the patient can afford it, whilst the alternative therapeutic option cannot be used because doctors are afraid of being sued and governments fear European law sanctions under the accusation that they are putting public health at risk. In fact, European law tends to allow off-label prescription only in the absence of a duly approved drug. However, this basic rule – which should indeed be the one that rules off-label prescription – was formulated for a different financial scenario in which the price of the approved drug could actually be paid. Of course that in the past there were some drugs whose price could hardly be afforded by the NHS; however, because the economic recourses available were higher it was assumed that governments should pay for the best therapeutic alternative. However, this is not the world in which we currently live. Therefore, if this premise fails – that is, if the MA drug cannot be paid for, at least not for all patients – this entire line of reasoning falls apart. As a result, and without denying the prevalence of ‘public health’, this basic value should receive a different understanding that fits the existing budget constraints. Otherwise, Europe will be stuck in a utopic comprehension of ‘public health’, without the ability to actually achieve it.

VII. The possible threat to patient safety And public health

The first premise to take into consideration in this analysis is that an MA does not offer an absolute guarantee of security. In other words, the existence of an MA does not imply that the drug is absolutely safe, because the evaluation that took place to grant the MA only took into consideration the restricted uses and the specific patients described in the MA request, not all hypothetical uses of the drug. However, even in regards to those restricted uses listed in the MA, the fact is that the MA cannot guarantee that the drug is

absolutely safe, and indeed, negative outcomes can always occur. In contrast, the off-label use of a drug does not necessarily lead to adverse events or automatically endanger patients. Actually, many drugs used off-label are very similar in composition to the licensed drugs. The reasons that manufacturers do not apply for an MA regarding a specific use frequently have nothing to do with the inability of the drug to be safe and effective for that particular use, but merely with the pharmaceutical company’s strategies, mostly related to legal and economic risk management. Nevertheless, the choice of a non-authorised drug can raise problems from the perspective of patient safety. Indeed, even duly approved drug uses cannot guarantee absolute safety, but the level of risk increases drastically with non-approved drug uses. Let us return to the case of Avastin and Lucentis. Studies show discrepancies regarding the possibility of adverse outcomes with Avastin compared to that with Lucentis. According to one study, the off-label use of prescription drugs has been identified as an important contributor to preventable adverse drug events in children. Despite concerns regarding adverse outcomes, no systematic investigation of the effects of off-label drug use in adult populations has yet been performed [17,54]. However, other studies maintain that although both drugs are equally effective, the possibility of adverse reactions is much higher with Avastin [31]. In addition, even if both products have the same level of safety and efficacy, the risks involved in drug manipulation would always recommend the use of Lucentis, and this ‘detail’ cannot be ignored in the assessment of the drug’s safety. The situation would probably be more transparent in terms of patient safety if a totally independent authority – that is, one not funded in any way by the pharmaceutical industry – could perform those studies. However, neither the EMA nor the national drug agencies of the EU Member States have the ability to do so. Another option would be to assign this task to health technology evaluators, such as the NICE in the United Kingdom and the Haute Autorité de Santé (HAS) in France. Whereas drug approval authorities are concerned only with the efficacy and safety of the product, these other entities also take financial appraisals into consideration, which are essential in this context, because the question is to evaluate

whether the benefit brought by those pricy drugs can justify the spending they demand (Editorial from *Nature Medicine* 2012). We can even follow the suggestion of Rodwin and impose the costs of those studies on the pharmaceutical companies because they are the ones that profit most from off-label use [17]. If off-label prescription becomes normal practice – grounded in economic considerations – then pharmaceutical companies may simply feel tempted to abandon the institutionalised model of compelling MA for every single drug use. Furthermore, the incentive to invest in research and development may disappear because companies will realise that their drugs are competing with other medical products that were exempted from the demanding MA procedure, and the final result could be a drastic diminution of the number of innovative drugs [55]. Nevertheless, it has long been recognised that in some particular scenarios off-label prescription corresponds to the best standard of care, and thus it is legally allowed. Financial constraints are not usually considered to be one of those specific scenarios, but in light of the rule of austerity dominating health care delivery, this exception, under certain requirements, should be accepted by national governments and by European law. In terms of patient safety, and assuming that the off-label drug satisfies the expectations of safety and efficiency, this is a better solution than simply depriving patient of any treatment. It cannot even be argued that pharmaceutical companies will decrease their revenues and consequently diminish investment in research and development, because the alternative option would be, quite simply, to not make any profit with the expensive drugs, which are not being purchased because they are not being used. Even if that were the case – that is, even if pharmaceutical companies were actually suffering an effective loss of profits from the off-label use of cheaper drugs – there could be no other solution, because it is obviously more important to guarantee patients access to medicines than to guarantee pharmaceutical companies access to profit. One could argue that less profit implies less investment in research for future drugs, and of

course no one wants to hypothesise on the well-being of future patients, that is, the ones who will potentially benefit from the future drugs that result from today's investment in research and development. However, that result – which is merely hypothetical – cannot be achieved at the expense of the well-being of today's patients, the threat to whose health is not potential but actual and effective.

VIII. Should economically motivated off-label prescription be banned?

There are many reasons in favour of off-label prescription. After all, sometimes this is the only available treatment, either for all patients with a particular medical condition or for a particular patient, because many off-label uses are innovative treatments that may correspond to the best standard of care. In addition, the developments that off-label prescription can bring for medical practice and pharmaceutical knowledge cannot be underestimated [56]. Pharmaceutical companies, in particular, require off-label prescription to increase their sales [17]. However, the legitimacy of off-label prescription exclusively grounded on economic considerations is very controversial. In addition to the critical issues already noted – violation of European rules and threat to patient safety – another argument to consider is protection of the pharmaceutical companies that comply with European rules; not only the protection of the companies themselves, but also and foremost, the protection of their research and development and of the decisive benefits that new drugs can bring. No one denies that developing a new drug is an extremely expensive task [57]. The spread of off-label promotion, especially when there is a properly authorised therapeutic option, will lead to a scenario in which pharmaceutical companies will no longer have the incentive to request MAs. In fact, the procedure of drug approval is costly and time consuming and requires a huge investment in human and material resources on the part of the pharmaceutical company. The company would not be willing to make such a huge investment without the expectation of profit. If the

competitors manage to put their products on the market without passing through this demanding procedure and can still achieve a high number of sales and huge profits, why not do the same? This will particularly be the case regarding orphan drugs, which would leave the patients who require these drugs without therapeutic options. Therefore, despite the fact that the demand for profit from the pharmaceutical companies does seem a futile aim, it is in fact a decisive one, because without profit, these companies will not develop new drugs. Moreover, from a legal point of view, European law has long proclaimed a 'general principle, identified in the case-law, that protection of public health must unquestionably take precedence over economic considerations' (*Artegodan GmbH and others*). Therefore, legal solutions that admit the use of a non-authorised medicine based exclusively upon cost considerations may be in contradiction with the entire system of drug authorisation settled by European law and with several ECJ rulings, namely, *Commission v. Poland*. Furthermore, from an ethical perspective, every patient is entitled to optimal health care and the failure to do so may violate the right to health care, which is a primordial fundamental and human right. In sum, there are several interests and goals to consider from both sides ^[58]. In the past, we have advocated the prohibition of off-label prescription whenever a drug has been approved for that particular medical use ^[5]. However, this conclusion depends on a basic premise: that financial austerity does not control health care delivery. In recent years, however, economic constraints have come to rule every medical decision, including the choice of drugs ^[59]. As a result, health budget constraints make it impossible to provide the best possible care to each patient with the best possible (authorised) drug. If health care resources are limited, both rationing and prioritisation are imperative. One of the rules imposed by efficiency – and actually by logic and common sense – in health care decisions is the priority of cheaper treatments over more expensive ones if both present the same level of effectiveness and safety. Therefore, we believe that in very specific scenarios of financial austerity, in which it is imperative to reduce health care expenses, the off-label prescription of cheaper drugs must be

allowed and reimbursed by NHSs, even if there is a duly authorised therapeutic alternative, but only if both medicinal products have equal levels of safety and effectiveness and the price difference is considered relevant. Is this the actual scenario of economic off-label prescription in Europe? First of all, not all European countries live at the same level of austerity, so this solution would only be allowed for the ones experiencing drastic austere measures. Second, it is imperative to have scientific data that demonstrates the equal therapeutic value of both drugs and that they have the same guarantees in terms of adverse drug events. Finally, the price difference also plays a decisive role, and only when this difference is 'relevant' should the off-label option take precedence. The adjective 'relevant' is used to give national governments the freedom to define this term and to set the level above which the price difference cannot be accepted. In this very particular scenario – but only when all requirements are fulfilled – should off-label prescription be allowed on the basis of economic motivations. European law does not currently provide sufficient legal grounds for this practice, and both the European lawmakers and the European courts continue to insist that public health should always prevail. Although in theory, no one can disagree with this basic principle, nowadays it is purely utopic, because in a bankrupt Europe (and probably in a bankrupt world), there is not enough money to pay for the best drug for every single patient (assuming that the properly approved drug is always the best one). Other possible measures could be to limit the profits of pharmaceutical companies or negotiate the price of the more expensive drugs to constrain health care expenditures; this article does not refuse any of these measures. This is not to say that to allow off-label prescription in the referred scenario would miraculously save national health services and guarantee proper medical care to every single patient (even because for some of them even the less expensive drug can be just too expensive), but this measure could certainly alleviate some of the economic pressure. In conclusion, economic considerations do have a role to play in health care, and in practical terms, it could not be any other way. However, they can never assume the lead in health care decisions.

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