Off-label use of medicinal products: a legal update

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Off-label use of medicinal products is an interesting and sometimes frustrating phenomenon from many perspectives. There may be very good reasons to prescribe an authorised medicinal product for a non-authorised patient group or for a non-authorised indication. On the other hand, this raises questions on the effectiveness of the regulatory system, not only with respect to pre-market approval, but also with respect to the development of medically important secondary applications of medicinal products. Off-label prescribing also has an impact on reimbursement of medicinal products.

This article examines the following:
- What is off-label use?
- Reasons for off-label use.
- Regulatory and other policies.
- The extent of off-label use.
- Off-label use and the healthcare professional.
- Off-label use and the pharmaceutical industry.
- Policy issues: reimbursement and substitution.
- The future of off-label use.

WHAT IS OFF-LABEL USE?

Scope
Marketing of medicinal products is highly regulated, but the use of medicinal products is not. In fact it can be argued that medicinal products figure in two completely different environments:

- The world of the pharmaceutical industry and health authorities, in which decisions on the scale of the entire population are taken.
- The world of the users and medical practice, where healthcare professionals and patients have to cope with individual medical conditions and treatments.

The area where the two environments do not overlap is the area of off-label use.

On-label prescribing
To define off-label use, a starting point is on-label use, the normal situation where medicinal products are used as foreseen at the time of authorisation. On-label use of a medicinal product is when physicians prescribe a drug for a patient according to authorised indications and taking into account contra-indications, based on the approved Summary of Product Characteristics (SmPC) (the document that is annexed to the marketing authorisation in the EU regulatory system), or label (in the US).

Marketing authorisation

Before a medicinal product can actually be marketed, the pharmaceutical company has to apply for a marketing authorisation. Obviously, availability of a medicinal product in the market is a prerequisite for off-label use, as it is a prerequisite for on-label use. Without marketing authorisation official product information or label would not exist, and discussions about off- or on-label would be pointless. Since the early 1960’s authorisation systems for medicinal products have been created all over the world, under which before marketing an assessment of safety and efficacy by government appointed experts takes place, and a marketing authorisation can be issued by the government. One of the best-known reasons for this is the Sotenon crisis, which occurred in Europe. Many pregnant women used thalidomide, which appeared to be teratogenic. Children of mothers who had used the drug were born malformed.

The basis for the marketing authorisation is the dossier that is submitted to the authorities by the applicant. The marketing authorisation dossier contains, in addition to administrative data, the results of chemical and pharmaceutical, toxicological, pharmacological and clinical tests and trials with the concerned medicinal product. The dossier requirements for a marketing authorisation are harmonised globally; the authorities and the industry associations of the main markets (the US, EU and Japan) have joined forces to create formats and dossier requirements for the evaluation of medicinal products, through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Common in all pre-market approval systems for medicinal products is the fact that the evaluation focuses on the risk/benefit ratio for a specific (set of) indication(s). The purpose of the assessment is primarily to keep unsafe products off the market and to limit the use to situations in which a certain level of efficacy is to be expected, balanced against safety issues for the particular indication. The contents of the dossier are the responsibility of the applicant, both the quality part and the evidence presented on safety and efficacy and the claims made based on the evidence presented. If a specific medicinal product has a broad scope of potential indications, the applicant can choose whether to apply for approval of all indications of the medicinal product at one time, or, if early market access is important, to launch the medicinal product for a narrow indication. In the latter case, the package of clinical trials to be submitted for assessment is obviously smaller.
Cross-border

Product information

The outcome of the evaluation by the authorities is reflected in two main documents: the marketing authorisation or approval letter (US), important because it marks the start of marketing of the product, and the approved product information. The approved product information consists of information for healthcare professionals and information for patients. The information for healthcare professionals (SmPC in Europe, labelling in the US), specifies all the claims that have been submitted by the applicant and approved by the authorities. Which potential uses of a specific medicinal product have been investigated and which indications are decided by the applicant for the marketing authorisation, not by the authority. The objectives of the pharmaceutical industry do not always run parallel with public health goals with respect to indications and populations medicinal products are being developed for. Reasons not to develop a drug for a specific indication or patient group can be lack of incentives and lack of possibilities to protect the investment. A company developing a specific important new indication for a medicinal product must consider the profit this would create. For older products, no patent protection is available, so the investment will benefit not only the investor, but the (generic) competitor as well.

It follows that inevitably on approval only part of the actual potential use of a medicinal product has been investigated in clinical trials.

Definition of off-label use

Off-label use is the practice of prescribing medicinal products outside the scope of the conditions of the marketing authorisation, reflected in the SmPC (or approved label), most often concerning indication and dosing, and especially for other patient groups, such as children. The use of an unauthorised medicine is not considered to be off-label use. Experimental use of a medicinal product, either in a clinical trial or outside of a clinical setting (approved by an ethics committee), is not considered to be off-label use either.

REASONS FOR OFF-LABEL USE

Temporary off-label use

It has been recognised that medical science is, of course, ever evolving. Applications of a specific active substance in the treatment may become feasible a long time after a medicinal product has been launched. These applications (indications or specific patient populations) have not been encompassed in the authorisation process, and are therefore not reflected in the product information. An example of this is the use of acetylsalicylic acid (Aspirin) as a thrombolytic.

Another important explanation for off-label use can be that a disease is treated in a “trial and error” approach. An example of this is the use of combinations of cytostatics for cancer patients in specific stages of the disease. Oncological treatment often has to be individualised, because of differences between patients with respect to the resistance to individual active substances of cancer cells.

A final general aspect relates to the slowness of assessment and authorisation of variations to a marketing authorisation. Long after a trial for a new indication has been successfully concluded, the authorisation procedure might still be in process.

Continuous off-label use

Apart from timing issues, the main reason for off-label use is the fact that a specific off-label use of a medicinal product has not been investigated, tested and authorised. The development of a medicinal product is extremely expensive. Figures in the range of US$1 billion (about EUR700 million) have been given (see Boston Consulting Group, A revolution in R&D: How Genomics and Genetics are Transforming the Biopharmaceutical Industry. (2001); and DiMasi, J, Hansen, RW and Grabowski, HG, The price of innovation: new estimates of drug development costs (2003)).

Paradoxically, although enormous amounts of money are spent on randomised clinical trials, only part of the useful applications of a medicinal product is investigated. The indications and the population for which medicinal products are being developed and investigated, are decided by the applicant for the marketing authorisation, not by the authority. The objectives of the pharmaceutical industry do not always run parallel with public health goals with respect to indications and populations medicinal products are being developed for. Reasons not to develop a drug for a specific indication or patient group can be lack of incentives and lack of possibilities to protect the investment. A company developing a specific important new indication for a medicinal product must consider the profit this would create. For older products, no patent protection is available, so the investment will benefit not only the investor, but the (generic) competitor as well.

Other reasons not to develop an application can be of a legal or practical nature. An example is the development of paediatric uses of a medicine. Clinical trials with children are more complicated than other clinical trials for ethical reasons. If a medicinal product is not authorised for paediatric use, liability for adverse events in children can be limited. For the use of medicinal products in pregnancy or lactation the same practical and ethical considerations are applicable.

Off-label use in medical practice

In the relationship between healthcare professionals and patients, individual treatment decisions have to be made in the best interest of the patient. Sometimes the best possible treatment is on-label use of a medicinal product, sometimes off-label drug use represents the best care, sometimes an alternative treatment is not available. Off-label use of medicinal products is therefore accepted all over the world (with possibly some exceptions, such as Hungary), as long as it is appropriate. In the recent Medicines Act in The Netherlands, off-label use is limited to cases where the use is either in line with standards or protocols, or where the prescriber has consulted a pharmacist (Article 68, Geneesmiddelenwet). The concept of what is appropriate is dealt with in more detail below (see below, Good and bad off-label use). The freedom of prescribing, under professional standards, not only allows physicians to prescribe off-label, but may even oblige them to do so, in situations where off-label use is the best possible treatment. An example of this situation was the decision of the Oberlandesgericht Köln of 30 May 1990 (27 U 169/87). The case concerned the off-label use of acyclovir to treat a herpes induced meningitis. The court decided that the patient had to be treated with acyclovir if it would be a necessary treatment, even if its use in this indication was not authorised.
**REGULATORY AND OTHER POLICIES**

**Regulatory policies**

The main goal of the regulatory system is to protect public health. The fact that medicinal products are used, even if this off-label use is completely appropriate, in areas that have never been subject to randomised clinical trials, proves the relativity of the golden standard in drug development. A comparison can be made with the creation of a very high fence (high standards in drug regulation), but leaving a big part of the area without any protection. Off-label use is largely regulated and lack of oversight may lead to negative health outcomes, as it did in the case of off-label use of encaidine and flecaainide. Both antiarrythmic drugs were used to prevent premature ventricular complexes, but were found later to increase patient mortality (A Patkar, D Holford, DF Brophy, M Pyles; Off-Label Prescribing of Eryptopoeisis-stimulating Proteins in US Hospitals; Drug Information Journal; 41 (2007) p. 431 to 440). Further, the small groups of documented off-label users makes the identification of uncommon, but serious, adverse drug reactions more difficult. An example is the risk of serious heart valve damage that is related to the off-label use of the combination (Fen-Phen) of fenfluramine (Pondimin) and phentermine for weight loss, which was discovered after thousands of patients had been exposed to this risk. (See: Henry, V, Off-Label Prescribing, Legal Implications, J. Leg. Med. 1999; 20 (3) p. 376).

It is obvious that regulatory authorities are cautious about off-label use, because it undermines their function as well as the effectiveness of their work. If medicinal products are used off-label, patients and healthcare professionals do not get the authorised information that is the major contribution of the regulatory system. Further, the information that is authorised may well have a different conclusion with respect to the risk/benefit ratio than the conclusion that would have been drawn for off-label uses.

Additionally, the fact that a medicinal product has not been tested (or at least, the results of testing have not been published or approved in an authorisation procedure), means that the authorities (or healthcare insurance companies) have no robust scientific data, as a basis for their decision making processes with respect to pricing and reimbursement.

**The US**

The Food and Drug Administration (FDA) introduced in 1972 an official policy with respect to off-label use called the “practice of medicine exemption”. This policy stated that a physician can, as part of the practice of medicine, lawfully vary the conditions of use from those approved in the package insert without informing or obtaining the approval of the FDA. The FDA repeatedly pointed out that off-label use is not experimental and can be rational and appropriate (Rayburn, Farmer, Off-Label Prescribing During Pregnancy, Obstet & Gynecol., Clin. N. Am. 471; Sept. 1997).

In 1997, Congress passed the Food and Drug Modernization Act, which abolished the prohibition of promotion of unapproved uses of drugs. FDMA allowed manufacturers to disseminate articles which abolished the prohibition of promotion of unapproved uses of drugs. FDMA allowed manufacturers to disseminate articles (or healthcare insurance companies) have no robust scientific data, as a basis for their decision making processes with respect to pricing and reimbursement.

**Initiatives**

Off-label use is characterised by the fact that a drug has not been authorised for a specific indication. In many regions, initiatives have been addressing this issue by encouraging the pharmaceutical industry to investigate unauthorised uses of their products. Legislation creating incentives for orphan medicinal products (drugs to treat rare diseases), can lead to authorised alternatives for off-label use (US: Orphan Drug Act, 1983; EU: Regulation (EC) No. 141/2000 on orphan medicinal products). Another area that is addressed is paediatrics. In the US and the EU, specific legislation has been established, creating obligations to investigate paediatric use of medicinal products and also compensating these obligations by granting a reward for the investments (US: Best Pharmaceuticals for Children Act, Public Law 107-109, January 4, 2002, EU: Regulation (EC) No. 1901/2006 on medicines for paediatric use).

In the US, drug use information can not only be derived from the labelling which has been approved by the FDA, but also from organisations like the United State Pharmacopeia (USP). Since the 2000 decision, information on off-label use can be obtained from this publication. In USP Drug Information, indications are listed in one of three categories: accepted, unaccepted or acceptance not established. The category of accepted indications contains not only the indications that have been authorised by the FDA (or Health Canada, the competent authority of Canada), but also off-label indications considered appropriate by USP Advisory Panels. The reason for this is that it is deemed important to disseminate information on evidence-based medicine for improved patient care (R.S. Blum, Legal Considerations in Off-label Medication Prescribing, Arch Intern Med, 2002 (162) 12/26, p. 1777-79).

Other organisations which publish acceptable guidance with respect to off-label use are Drugdex by Thompson Corporation and AHFS Drug Information by the American Society of Health-Systems Pharmacists. If a specific off-label use is listed in any of these three publications, Medicare accepts insurance coverage.

**EU**

The health authorities in Europe have ignored the topic of off-label use to a large extent. In the EU, direct-to-consumer advertising is prohibited, at least for prescription medicines. Promotion of medicinal products to healthcare professionals is strictly limited to the information that is contained in the authorised product information, SmPC (Article 88, paragraph 1, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Code for Human Medicines Directive)). Authorities tend to be very silent about the uses of medicinal products for which they do not have (clinical) data on file, so for which it is impossible to give a scientific assessment. In Germany some discussion has started with respect to off-label use. This is based on an important ruling of the Federal Court for Social Affairs relating to the reimbursement of medicinal products which were used elf-label (Bundessozialgericht, 19 March 2002, B1 KR 37/00 R). The topic has not been discussed among the competent authorities, for example in the European Medicines Agency (EMEA), outside the scope of pharmacovigilance.
For many of the indications and patient groups for which medicinal products are used off-label, these type of incentives do not apply: the development of older products for new indications or populations lacks adequate patent protection. Patents for new indications of an existing medicinal product do not protect against generic competition. A generic version of a medicinal product will normally be used for the same indications as the innovator product of which it is a copy. The alternative protection by regulatory data protection does not work either, since two rulings of the ECJ established that new indications, new target populations or new pharmaceutical forms are not protected (Generics (ECJ 8 December 1998, C-368/96); Novartis (ECJ 29 April 2004, C-106/01)).

As compensation, the EU legislator offers only one year additional regulatory data protection, if an important new indication enables the company to recover the investments for the authorisation of the new indication.

THE EXTENT OF OFF-LABEL USE

Numbers

Scientific data on off-label use are not readily available. There may be some bias in reporting by physicians, because of the notion, stronger in the past than today, that off-label use is not in line with professional standards. In some specific areas, like paediatrics, the percentage could be as high as 90%. In oncology, large numbers can be expected as well. 56% of cancer patients have been given non-FDA-approved prescriptions and 33% of all prescriptions in cancer treatment were off-label. In general practices, percentages around 20% have been found. 81% of AIDS patients received at least one drug off-label and 40% of all reported drug use was off-label. An overall estimate of off-label use could be 50%.

Examples of off-label use

The situations in which off-label prescribing occurs can be divided in the following categories according to the reason for the decision:

- (Perceived) best alternative.
- Better price.
- Patient's preference (for other reasons).

In relation to the best alternative, a further subdivision can be made. It is obvious that off-label use is the best alternative if there is no treatment available. This would most likely be the case in many paediatric and oncological indications, but it could be the case for other orphan indications as well. If patents and other intellectual property rights have expired, there is no incentive to develop a medicinal product and to change off-label use into an authorised use. The consequence is that also in not so rare indications, a lack of alternatives can be perceived. An example of this would be the use of nifedipine (Adalat) as tocolytic (labour inhibitor). Another example is the use of gabapentin (Neurontin) for off-label indications. Gabapentin is discussed further below (see below, Promotional aspects).

Sometimes, evidence-based medicine is far ahead of marketing authorisation procedures: the medical world may have accepted the beneficial effect of the use of a medicinal product long before health authorities have been able to take their official decisions. An example of this is the use of clopidrogel (Plavix) for the prevention of cardiac complications after elective stenting. Early broad use of rofecoxib (Vioxx) and other COX-2-inhibitors is an example of the use of medicinal products “by analogy”. These drugs were supposed to have a better safety profile compared to older NSAIDs (category of nonstereoidal anti-inflammatory drugs), regarding gastrointestinal side effects. Even though the COX-2 inhibitors were authorised for a limited indication, they were used for many indications instead of the older NSAIDs. Ultimately, this widespread use brought the holder of Vioxx marketing authorisation into serious problems, when cardiac safety of the drug became the object of FDA and EMEA inquiries.

An example where off-label use is caused by budget pressure from healthcare insurers and hospital management is the Avastin/Lucentis case. Bevacizumab (Avastin) in wet macula degeneration is used instead of ranibizumab (Lucentis). Both Avastin and Lucentis inhibit the action of vascular endothelial growth factor (VEGF). Avastin is an anti-body that has been authorised for colon cancer. Lucentis is an antibody fragment that is authorised specifically for wet macula degeneration. Because of the price difference, many hospitals substitute Lucentis with Avastin.

With respect to personal considerations of patients, a preference for an off-label use over an authorised use of another medicinal product can be expected, for example, in cases where the patient has previous experience with the off-label product and does not want to change.

OFF-LABEL USE AND THE HEALTHCARE PROFESSIONAL

Good and bad off-label use

In the 1990’s, off-label use was recognised as a necessary instrument for the treatment of patients in both the EU and the US. Examples can be found in many places in US Case Law and literature (see Richardson v Miller, 44 S.W.3d, n.11 (Tenn. Ct App. 2000) and Beck & Azari, 53 Food & Drug L.J., p.71-72). In scientific literature, the terms “appropriate” and “inappropriate” off-label use are often discussed. The main conclusion is that to be appropriate the off-label treatment has to be the best possible treatment for the patient. However, the problem is that, contrary to on-label use, off-label treatments have not always been the subject of randomised clinical trials. The evidence with respect to the risk/benefit ratio for off-label use can therefore not be at the same level as the evidence in the dossier that is submitted for a marketing authorisation. Where off-label use is practised it is done so on an individual basis, whereas on-label use is part of the regulatory regime, where decisions on safety and efficacy are based on clinical trials with larger groups of patients.

Some prerequisites for appropriate off-label use include the following questions:

- Is there an authorised alternative available?
Is there enough evidence to assume that the off-label treatment might be effective? There are different levels of acceptable evidence, for example, papers in peer-reviewed journals are more important than the views of a single expert on the merits of the treatment.

Has the existence of serious adverse drug reactions been ruled out?

Does the patient consent to the off-label treatment, after having been given all available information on alternatives, risks and benefits?

**Authorised alternative available**

If a prescriber has to choose between an on-label and an off-label treatment, the authorised alternative would normally be the best possible care. Only under exceptional circumstances could there be a medical advantage for an individual patient to choose off-label treatment. The latter implies that a preventable risk is taken.

**Level of evidence**

To be considered as appropriate off-label use, it is also important to define the level of scientific evidence about the efficacy and the safety of a medicinal product. In the case of off-label use, the prescriber must decide on the risk/benefit ratio for the individual patient, whereas this assessment is made by the health authorities for the authorised indications.

The big difference between the use of a drug within the terms of a marketing authorisation or off-label use is the level of assurance the physician can rely on when he decides to prescribe the product. Authorised medicines have been investigated and tested extensively, before health authorities draw a conclusion about the balance of the desired and undesired effects of the drug. The burden of responsibility for the choice of off-label treatments is heavy on the prescriber, while most of this responsibility is on the authorities and the manufacturer in the normal situation.

Evidence-based medicine is a more time-consuming activity if off-label use is part of the treatment. Medical literature probably plays a more important role in assessing the appropriateness of treating a patient off-label. Other issues of a medical nature include the dosing of the drug: if no marketing authorisation exists for a specific indication, dosing sometimes has to be done on the basis of trial and error.

**Adverse events**

There is always the chance that a side effect (adverse drug reaction) will surface in the patient that is treated. If the adverse drug reactions is of a serious nature, questions around liability can emerge: is the off-label prescription within the limits of the standard of care, or can it be considered as malpractice?

**(Written) informed consent**

The principle of informed consent is extremely important in these situations. The treatment, its risks and benefits, the alternatives and the off-label character of the treatment must be discussed extensively with the patient. A Dutch disciplinary tribunal decided in a situation where the off-label use of nifedipine as a labour inhibitor was completely appropriate, that the physician was wrong where he did not gain (written) informed consent of the patient (Centraal Medisch Tuchtcollege, 10 February 1998).

**Liability**

While the practice of using drugs off-label is widespread and not inherently inappropriate, there are well-documented instances where an accepted and popular off-label use of medicine has ultimately proved to be harmful. Physicians can be found negligent if their decision to use a drug off-label is sufficiently careless, imprudent or unprofessional. This means that a doctor can act professionally in the best interest of patients when prescribing off-label. However, if something goes wrong with a patient that has been treated off-label, questions around neglect and malpractice come up immediately. In our opinion there is no reason to have a different type of legal approach towards physicians, just because the treatment was within the label or off-label. Or said differently: on-label use and appropriate off-label use are always allowed, where bad prescribing is never allowed. Bad prescribing is not limited to off-label use but could also occur within the label.

If a patient is injured after off-label treatment, the patient has to prove that the physician did not act within the applicable standards of care. The physician has the obligation to provide facts about the treatment, such as the care and consideration that have been exercised in the decision for the off-label therapy. Again the level of evidence supporting the off-label use is relevant. Hospita- l or scientific standards including the off-label treatment could support the appropriateness of the off-label treatment as well. However, the informed consent of the patient is the most important element. In the case of off-label prescribing therefore, the consent should always be given in written form.

Another healthcare professional who could play a role with respect to off-label prescribing is the pharmacist. Both in hospital and in community pharmacies the pharmacist could be involved in the decision, being trained in pharmaceutical care. In the Dutch legislation the dispensing pharmacist has to be consulted before an off-label prescribed medicine can be dispensed in situations where the treatment has not been taken up in professional standards.

**OFF-LABEL USE AND THE PHARMACEUTICAL INDUSTRY**

**Promotional aspects**

The promotion of off-label use of medicinal products is prohibited in all jurisdictions for obvious reasons. Why would a company bother to do the extensive testing necessary to authorise a new indication if he can sell the product for off-label use anyway? Further, the off-label use of a medicinal product may not be approved if an application is submitted to the health authorities.

In the US, cases of off-label promotion regularly reach the headlines of the newspapers. An example is the lawsuit against Warner-Lambert with respect to off-label promotion of gabapentin. In May 2004, Warner-Lambert admitted guilt and agreed to pay US$430 million (about EUR301 million) in relation to criminal and civil liability regarding the promotion of gabapentin for uses not approved by the FDA. The promotional activities investigated
were in the field of continuing medical education and research. This case shows that there is a thin line between scientific and commercial activity, especially in the field of off-label medicines. (M.A. Steinman et al; Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents; Annals of Internal Medicine; 145 (2006) 4, p. 284 to 293.)

Medical practitioners and healthcare insurers are, however, not bound by such rules, and off-label treatment can be recommended in treatment guidelines (solely) for reasons of cost. Healthcare insurers offer bonuses to general practitioners and hospitals alike to prescribe only the cheaper substances in a class of products for the vast majority of patients, sometimes regardless of specific approved indications.

Product liability
The fact that a medicinal product is authorised for a specific indication or population does not pre-empt a product liability claim for off-label use. A manufacturer might, for example, be liable if he did not provide adequate warnings for risks associated with reasonably foreseeable off-label use of his product. This means a manufacturer has to investigate the use, including foreseeable “misuse”, of his product and the risks involved, before he puts it on the market. But even if during pre-marketing investigation off-label use was not reasonably foreseeable, a manufacturer can be liable for off-label use. For instance, when the manufacturer knows, or should have known, about the post-marketing off-label use and did not warn about the associated risks.

The liability of the manufacturer towards the injured patient is not reduced if the damage has been caused both by a defect in the product (inadequate warning) and by the conduct of the physician (off-label use not according to the applicable standards of care).

POLICY ISSUES: REIMBURSEMENT AND SUBSTITUTION

Reimbursement
As explained above (see above, Examples of off-label use), off-label prescription is allowed and even recommended throughout the EU if it is the best treatment for the patient and alternative authorised treatments are not available. General costs of healthcare or budget control of a hospital alone can therefore never be a reason for off-label use.

Further, off-label use requires a joint decision by the individual patient and his physician. Decisions by government authorities and their advisory bodies in respect of reimbursement of the cost of the medicinal product under any social healthcare system are, however, never based on individual considerations but on the scale of the entire population.

The conflict between these two worlds, the individual patient and his doctor on the one hand and government authorities and healthcare insurers on the other, arises in various areas of reimbursement. The first issue that arises is whether a medicinal product is reimbursed for all indications for which the healthcare professional deems it appropriate or only for the authorised indications. Often, older, cheaper products are reimbursed for authorised and non-authorised use, whereas reimbursement of new and more expensive treatments is sometimes strictly limited to the authorised indication(s).

Equally, in various EU member states hospitals receive additional financing to enable them to use new and expensive treatments in serious indications. In most cases this funding only partly covers all costs. The trastuzumab (Herceptin) example, which was discussed in many jurisdictions, is an example of such treatment. However, this additional financing is often limited to use in the authorised indication. If the hospital wishes to use the product for other indications, it is assumed by the payers that this can be financed from the “normal” budget. This often poses problems for the hospitals, because more than 50% of prescriptions is off-label and the budget is often not sufficient to pay for this. This leads to inequality between patients or so-called “zip-code medicine”, where availability of medicinal products depends on which hospital the patient is treated in.

While governments seem to be increasingly reluctant to reimburse new and more expensive medicinal products for off-label use, they are less reluctant to use off-label treatment as a comparator in the assessment of the therapeutic benefit in the context of reimbursement decisions for new products.

In The Netherlands for instance, the government takes the position that if off-label treatment is included in the professional guidelines of the relevant healthcare professionals, the marketing authorisation holder of the new product for which reimbursement is sought, may be required to present direct or indirect evidence of added therapeutic benefit of the off-label treatment. This line of thinking arguably has serious flaws. While it may be correct that for certain patients off-label use is the only option and as such “best medical practice” on the basis of individual considerations, this is often not enough to place the treatment on the same level as an authorised indication which has been researched and evaluated for the total population. For example, varenicline (Champix) is authorised for quitting smoking. Because the professional guidelines mention the old, even obsolete, antidepressant nortriptyline as a treatment option if other treatments fail, the marketing authorisation holder was required to make a therapeutic and pharma-economic comparison with nortriptyline, regardless of the facts that nortriptyline was only used for this off-label indication in 2% of patients.

In seems inconsistent for health authorities to be making decisions on reimbursement for a potentially large patient population based on off-label use which is only allowed on the basis of individual decisions by doctor and patient with specific informed consent of the patient.

Substitution
A related issue is therapeutic substitution by the physician. Therapeutic substitution is the replacement by the doctor of medicinal products with a different active substance, often a product belonging to the same therapeutic class. The result of this form of substitution is off-label prescription. Substitution decisions are usually a result of budget pressure, either from the healthcare insurer or hospital management.

Products from the same class have different authorised indications or contra-indications and in case of therapeutic substitution it is considered that this is irrelevant because a “class-effect”...
can be assumed. Although sometimes class-effects can be proven, often enough there is scientific debate on whether sufficient proof of such effects exists and what should be the correct test to assume this. This becomes even more relevant if additional factors come into play, for instance the route of administration.

In the example of Avastin and Lucentis this is particularly relevant as Lucentis is specifically formulated to be administered in the eye and Avastin is not. Further, specific risk management obligations exist for Lucentis, and not for Avastin. Even if consent for off-label use is obtained from the patient, it is questionable whether he can be adequately informed and how this can be the best available treatment for that particular patient. General costs of healthcare are not a factor to be discussed between doctor and patient when considering off-label use of a medicinal product. However, in decisions about reimbursement and hospital funding this seems to be the most important element.

THE FUTURE OF OFF-LABEL PRESCRIBING

Off-label use is here to stay. As long as there is no complete overlap between the interests and drivers in the regulatory world and the world of medical practice, off-label treatment will be necessary. Of course, the extent of off-label use should be diminished, because our regulatory system should protect as many patients as possible, by enabling physicians to use well-tested medicinal products to treat their patients. Incentives like the paediatric and orphan drugs legislation should be available for other medicinal products, to encompass more applications of medicinal products in the authorised domain.

For healthcare professionals the most important aspect of off-label use is awareness of their specific responsibilities to their patients. Off-label use should be limited to situations where it is appropriate, that is, the best possible care for the patient. Questions around the availability of an authorised alternative, the evidence of efficacy and lack of serious risks and the informed consent of the patient, should be answered before prescribing.

For the pharmaceutical industry, off-label use should remain a point of attention as well. Side effects of medicinal products do not only occur in on-label situations, but also when their products are used off-label. This should also lead to vigilance at the level of health authorities.

The most important factor of off-label use is policy. As marketing of medicinal products is vigorously regulated worldwide, governments should use their efforts to promote the development of medicinal products for indications that are not covered by authorised medicinal products. Instruments for this could be:

- Creating incentives for the industry to develop new indications for their products.
- Allowing reimbursement of authorised medicinal products, even if they are priced higher than an off-label alternative.

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