Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
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SYNTHESIS

TOWARDS A BETTER MANAGED OFF-LABEL USE OF DRUGS

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CELINE VANNIEUWENHUYSEN, PIERRE SLEGERS, MATTIAS NEYT, FRANK HULSTAERT, SABINE STORDEUR, IRINA CLEEMPUT, IRM VINCK

FOREWORD

Musicians, even when they are very good, can suffer from considerable stage fright. Apart from the discussion whether this problem should be considered as a 'real' disease or not, this mental state can sometimes get so bad that people become genuinely incapable of performing. Luckily a single tablet of Inderal® half an hour before the start of a concert can do miracles. Stage fright is however not indicated on the patient information leaflet of this classic beta-blocker, and therefore this particular use is a so-called 'off-label' use. Does this mean that physicians should not prescribe such drugs, even when their patients clearly benefit from them? And are health insurers allowed to reimburse such off-label use? In any event, this approach turns out to be much less expensive than other therapies, and certainly less expensive than long-term work incapacity. And what does Europe have to say about this?

A complex issue is lurking behind this rather innocent example a head-on collision between three different conceptual frameworks and values systems.

In a doctor-patient relationship, it is assumed that the doctor will do everything in his power to help or cure his patient, including things that are not entirely done by the book – or by the patient information leaflet, as the case may be – as long as they can be rationally justified.

Health insurers can largely concur with that, as long as the balance of the entire system is not compromised. After all, they also must take into account the cost-effectiveness and budgetary impact of reimbursement decisions, and they are aiming at an optimal use of every available euro. Therefore, from this public health point of view, it seems perfectly justified to support judicious off-label use in certain cases.

But this is where European legal barriers come in. These barriers have been set up to protect manufacturers' interests, for instance in cases where off-label use is prescribed as a less expensive alternative to a more expensive therapy, for the sole purpose of cutting expenditure.

In this report we will explore the thin line between clinical ethics, public health and the economy. And if sometimes we go a little over the line, we hope that, by doing so, we will contribute to a critical re-examination of some of the choices made to achieve that difficult balance between an economically strong and a socially-minded Europe. As far as we are concerned, this modest contribution to the debate is an attempt to give voice to the interests of public health and the patients.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

LIST OF ABBREVIATIONS

Abbreviation	Definition
AMD	Wet age-related macular degeneration
BCFI	Belgian Centre for Pharmacotherapeutic Information
EMA	European Medicines Agency
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
FDA	U.S. Food and Drug Administration
HIV	Human immunodeficiency virus
IGZ	Inspectie voor de Gezondheidszorg
MA	Marketing authorisation
MFC	Medico-Pharmaceutical Committee
NIHDI	National Institute for Health and Disability Insurance
SSF	Special Solidarity Fund
STAMP	Safe and Timely Access to Medicines for Patients

ABSTRACT

BACKGROUND AND CONTEXT

- Drug marketing and prescription in Europe is based on the idea of prior marketing authorisation (MA) of the medicinal product. This is based on an evaluation of the scientific data on the quality, safety and efficacy of the product. Since the marketing authorisation is based on the content of the dossier that is submitted to the authorities by the applicant, an indication or a modality of use that is not claimed by the applicant (called off-label use) will not feature in the package insert, unless it is listed as a contraindication or warning.
- The European pharmaceutical regulatory framework foresees in restrictive exceptions to the MA requirement. Off-label use comes within the scope of a number of these exceptions.
- Scientific evidence on off-label use is sometimes lacking. Yet, off-label use is widespread in clinical practice, in particular in oncology and paediatrics where off-label prescriptions are often the sole option. Information on the precise extent of off-label use is also lacking a.o. because physicians are not obliged to centrally register the off-label use.
- For pharmaceutical companies there may be a lack of legal and economic incentives to develop new indications or variations of existing indications. On the European level, measures have been taken to encourage extensions of existing MAs and to support research on new indications of authorised pharmaceuticals.
- From a scientific and social point of view, it may be desirable to develop knowledge on the off-label use of a pharmaceutical. Non-industrial researchers-sponsors are allowed to carry out studies. Obtaining a MA, however, is only possible if they can prepare a solid MA dossier. They may, however, have no access to the quality data and the non-clincal data (e.g. data on the production process). Moreover, it is not obvious to have access to the pharmaceutical, unless the non-industrial sponsor finances it himself.

LIABILITY

- The choice of therapy is primarily the physician's responsibility. The off-label use of medicines is covered by the legally recognized principle of the therapeutic freedom. Off-label use is lawful if the medication is prescribed with the care, skill and forethought of a medical practitioner in the same circumstances. To evaluate this, the scientific basis plays an important role. Furthermore, physicians are hold to explicitly inform the patient in advance and the latter needs to consent to the off-label use.
- A producer risks to be held liable if he ommited to warn for possible adverse reactions in association with an off-label use he was aware of or could reasonably have expected or which he actively promoted (wich is illegal). The application of the pharmacovigilance rules to off-label used products suggest that off-label use of a medicinal product is a "use to which it could reasonably be expected that the product would be put". It is unlikely, however, that the producer will be held liable if the patient was sufficiently informed on the possible risks by the package leaflet and by the physician and if the injury was not caused by a defect inherent to the product or an error in the leaflet.
- Pharmacists can be held liable for damage caused by a defective magistral formula. They are responsible for the quality of the magistral formula: correct weighing, right products, product imperfections,… Pharmacists must properly inform their customers about the off-label use of a medicinal product. They can check the off-label use if it relates to the patient group (children, pregnant women,…), dose and route of administration, but not the indication. In that sense, the risk of liability for the failure to advise customers on an off-label use which they could not have been aware of is fairly slim.
- National authorities can implement policy measures related to off-label use if they do not undermine the European pharmaceutical legal framework. This implies that they cannot take measures that detract from the effectiveness of the MA and the rights attached to it. Off-label prescribing remains the individual responsibility of a physician and policy measures may not counteract this. National authorities promoting off-label use for cost-considerations, could be held liable.

MEMBER STATES' POLICY OPTIONS FOR OFF-LABEL USE

- Commercial promotion of off-label used pharmaceuticals by producers, such as organising training sessions, recommending off-label use to physicians or pharmacists, financing research or grants for marketing purposes is not allowed. Health policy defined by a Member State does not pursue any commercial aim. Therefore, a financial incentive that forms part of such a policy, such as the reimbursement of a pharmaceutical cannot be regarded as commercial promotion. Yet, the national authorities should refrain from taking actions that would undermine the effectiveness of the pharmaceutical and other European regulation. Member States are free, however, to provide neutral scientific information regarding off-label used products.
- Member States are vested with the powers to set the reimbursement policy within the domain of healthcare. As such, they are free to reimburse off-label use to make them available when prescribed by a physician in an individual case. Measures supporting off-label use grounded on economic and budgetary reasons are not allowed.
- Based on the foregoing and from a societal point of view, national authorities can diffuse neutral scientific information combined with a reimbursement policy to render off-label use possible under the responsibility of a physician.

SYNTHESIS

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1. INTRODUCTION

1.1. What is off-label use?

Before medicinal products can be brought onto the European market, the producer must obtain marketing authorisation (MA) from the competent authorities (see frame "Who grants marketing authorisation?"). In his application file, the applicant will need to demonstrate that his product is of sound quality, safe and effective. To do so, the applicant will base himself on non-clinical (production process and pre-clinical studies such as animal testing) and clinical trials (testing in humans). The application file must also list the conditions which the product is indicated for, its composition and pharmaceutical form, the patient categories, route of administration, contraindications, dosage, etc. For this report, the notion "application" will be used when referring to one or more of these elements.

If the application file is approved, the applicant receives an MA and his product is classified as an **authorised medicinal product**. The summary of the product characteristics and the leaflet (label), produced on the basis of the summary list the approved uses of the medicinal product. However, if a medicinal product is used above the authorised dosage, in an unapproved age/patient group, for an unapproved therapeutic indication and/or route of administration, we talk about **off-label use**. Off-label use can occur for expensive as well as for cheap pharmaceuticals.

Off-label use is not uncommon in the run-up phase to an MA, or in certain situations (e.g. within the framework of a medical need programme, see below). In addition, off-label used medicinal products are also prescribed in routine medical practice.

Therapeutic indications

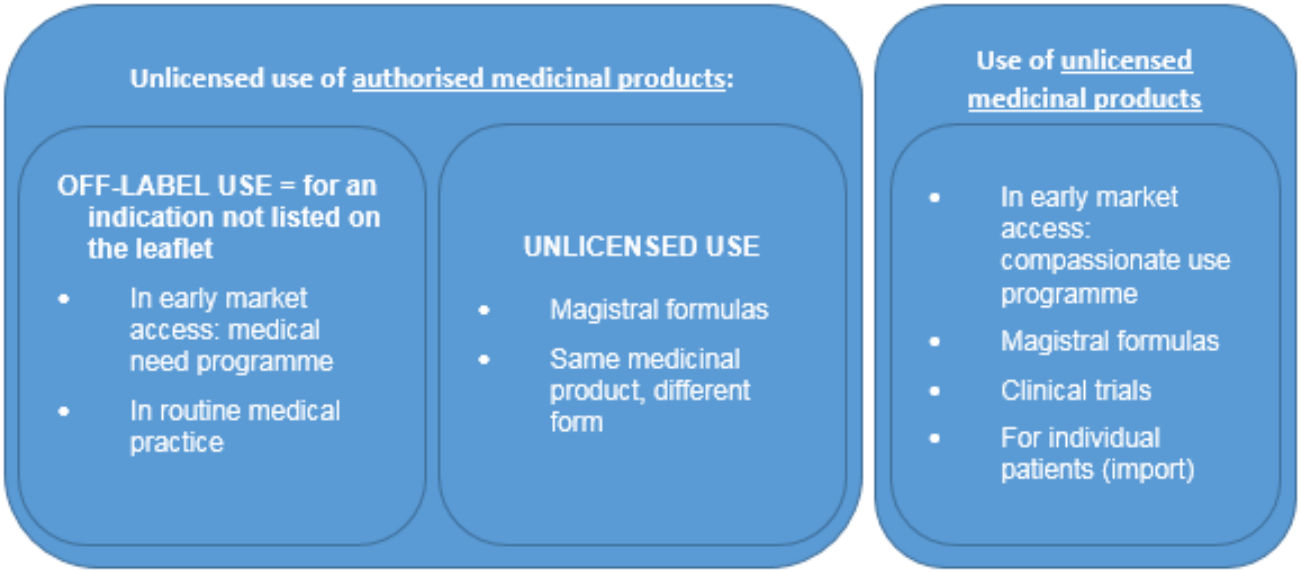
Each study/trial focuses on a specific group of patients, with specific characteristics, among which a well-defined pathology. It is on the basis of these characteristics, object of the study/trial in question, that an MA is applied for. This is known as the 'therapeutic indication' and is listed on the leaflet. For instance, an applicant can obtain an MA for a drug for 'patients aged 18 years and over suffering from metastatic colon cancer'.

A **new indication** can be a changed or new use of the medicinal product, e.g.:

- for a new condition
- for different pathologic stages or severity of the condition
- for a different age category
- from first to second-line therapy, or from a combination therapy to monotherapy and vice versa, or in a different combination (in oncology for instance)

The use of authorised medicinal products in unauthorised form is a different scenario again and is known as **unlicensed or unauthorised use**. Preparations by a pharmacist (magistral formulas) and modifications to the authorised form, such as processing tablets into a liquid to be administered orally are qualified as unlicensed use. So, medicinal products can be used both off-label and unlicensed if they are offered for a different indication and in a form other than the one(s) specified on the leaflet for instance.

In the case of the aforementioned off-label and unlicensed use, the MA of medicinal products authorised already is deviated from. **In addition, medicinal products that have not been authorised yet are also used** (see frame below). This can be the case in clinical trials or in "compassionate use programmes" for patients suffering from a serious condition for which there is as yet no drug on the market but for which either an MA is pending or clinical trials for the indication in question are under way.



***Comment**: In scientific literature the above distinction is not always as clear as it might. Also in this report, off-label is used as an overarching term. The term refers both to off-label use and to the unlicensed use of authorised medicinal products.*

Who grants marketing authorisation (MA)?

The European system that regulates the granting of MAs for medicinal products for human and veterinary use has been implemented to give EU citizens swift access to safe, effective and high-quality medicinal products.

To that effect, various procedures were put in place:[1]

- The **centralised procedure,** where applications are filed with the European Medicines Agency - EMA directly. Once the EMA Scientific Committee has approved an application, the European Commission can grant an authorisation that is valid across all the Member States. This procedure is mandatory for medicinal products containing a new active substance used to treat HIV, cancer, neurodegenerative disorders and diabetes. This procedure also applies for biotechnology products and for orphan drugs. Applicants are free to follow this procedure for other medicinal products also, if these contain a new active substance or an important innovation.
- In addition, each EU Member State has its **own, national authorisation procedure** for medicinal products that do not come under the compulsory centralised procedure. In Belgium, MAs must be applied for to the Federal Agency for Medicines and Health Products (FAMHP), the Belgian competent authority. Following a positive evaluation, the applicant receives an MA albeit valid for the Belgian market only.

In addition, there are also two variants, both of which are designed to obtain a harmonised MA, but these are not obtained via a central European body[a]:

- The decentralised procedure, where the manufacturer files his application with various Member States simultaneously. In this instance, the file is processed by one Member State and the other Member States can follow that Member State's decision.
- The mutual recognition procedure, where the applicant has obtained an MA from at least one European Member State already and then asks the other Member States to follow the decision of the Member State in question and to authorise the product.

An MA file comprises three sections that are assessed by the competent authorities (FAMHP for Belgium/EMA): quality of the pharmaceutical, non-clinical tests and clinical trials. The first two parts are not public, in contrast with the clinical trials that are summarised by EMA in European Public Assessment Reports.

1.2. Why are medicinal products used off-label?

Whereas the pharmaceutical company decides which indication it submits an MA application for, doctors are "free" (under conditions, see 4.2) to decide on the best possible treatment for an individual patient. Doctors are bound by deontology to prescribe the best option for their patients. This can conflict with the question of off-label used pharmaceuticals as will be further elaborated in this text. However, as soon as a medicinal product is approved for one specific indication, doctors are also free to prescribe it for other indications. Doctors may resort to off-label use if the standard therapy does not help, e.g. in certain types of cancer that are treated with (off-label) combinations of medicinal products. Sometimes, there are simply no authorised drugs available or they may be available but have not been authorised for use by certain patient(s) (groups) such as children, pregnant women or people suffering from a rare condition. If there are indications that the off-label use is effective in cases like these, the health of the patients in question could actually be put at risk if these drugs are not prescribed.

[a] This applies for most case where Member States agree. In case of persistent disputes, the case can be submitted to the "Coordination group for mutual recognition and Decentralised procedures" and if necessary via the "Committee for Medicinal Products for Human Use" to the EMA who gives a final advise.

At times, a medicinal product can also be used off-label to facilitate early access for seriously ill patients. In the period preceding an MA, **compassionate use or medical need programmes** can be availed of in circumstances like these. A compassionate use programme involves the use of a new medicinal product that has not been authorised yet, while a medical need programme entails using an authorised medicinal product for an indication other than the one the MA was granted for.

Both programmes are designed for patients suffering from a seriously debilitating or life-threatening chronic illness which cannot be properly treated with an authorised medicinal product or in an authorised indication. The (off-label) use of drugs within these programmes invariably requires the approval and support of the sponsor of the clinical trials or the MA holder, which tends to be the producer. Both these programmes are governed by a specific procedure (see 5.1.1).

Yet, in certain situations, doctors may sometimes opt for off-label use anyhow even if there are **authorised and effective alternatives** available. They may do so because the authorised drug is not reimbursed as it is considerably more expensive (see frame), or because it is only reimbursed for a (too) limited treatment duration or because the authorised alternative is in short supply (e.g. insufficient stocks) or because the treating physician feels that it is less suitable than the off-label product.

The use of generic drugs can also lead to **unintentional off-label use**. Often, generics of one and the same molecule list different applications on the leaflet. Even between countries, applications for one and the same generic can differ. Doctors are usually not aware of this. In countries, where pharmacists are free or obliged to substitute one medicinal product for a similar product, as is the case in Belgium under certain circumstances, this can sometimes lead to accidental off-label use.

The obligation on pharmacists in Belgium to supply patients who have been prescribed antibiotics or antimycotics (for the treatment of fungal infections) in acute treatment with the cheapest medicinal products and generic-name prescriptions can have the same effect. Sometimes, the cheapest product will not have the same authorised applications as the reference product.

Some examples of different modalities (expensive, cheap, often used, orphan) of off-label use in Belgium:

Frequent off-label use in routine practice

- Beta blockers are frequently used in stress situations e.g. in case of stage fright.
- Antipsychotics are frequently used in rest homes for elderly people coping with dementia and behavioural problems.[2]

Differences in label between Europe (EMA) and the USA (FDA)

This example relates to combinations of targeted therapies in oncology, i.e. for the treatment of metastasized melanoma with a BRAF V600 mutation. The pharmaceutical, dabrafenib (Tafinlar) is on the market for that indication in Europe as well as in the USA. The combination with trametinib (Mekinist) is now on the market in the USA based on phase 1 and 2 study results but was until today not authorised by EMA. In contrast with the USA, the use of this combination of pharmaceuticals is thus off-label in Europe. The reverse can occur as well.

Choice for off-label instead of an orphan drug that is not available in Belgium

Hydroxycarbamide is the active ingredient of two medicinal products that are registered for different indications. The first one, Siklos, has the status of orphan drug and is the only medicine with the registered indication of preventing vaso-occlusive crises in patients suffering from sickle cell anaemia. However, Siklos is not on the market in Belgium with the result that it is not reimbursed. For that reason the other drug, Hydrea, which is amongst others indicated for leukaemia, is used off-label to treat sickle cell anaemia. Siklos is also far more expensive than Hydrea: Siklos costs 14,525 euro per patient a year while Hydrea only costs 346 euro (Zorginstituut Nederland figures).[b]

Choice for the cheapest off-label medicine

Caffeine Sterop 25mg/2ml and Peyona (the latter is registered as an orphan drug) are indicated for the 'treatment of apnoea in premature newborns". Yet, both are used off-label to prevent apnoea in premature babies. Peyona is more expensive and must be covered by the parents because it is an orphan drug and, as a result, does not qualify for the lump sum hospital scheme. For that reason, the off-label use of the cheaper Caffeine Sterop 25mg/2ml is opted for.

Choice for a cheaper off-label alternative instead of a more expensive orphan drug

At present, several generics of Viagra (sildenafil) indicated for "erectile dysfunction of miscellaneous origins" are available on the market. That same molecule sildenafil is also recognised as an orphan medicine (Revatio) and is reimbursed by the health insurance to treat patients suffering from abnormally high blood pressure in the pulmonary artery (pulmonary arterial hypertension - primary or associated). However, the health insurance does not intervene if the medicinal product is administered for the secondary forms of this condition. For that reason, Viagra or one of its generics are sometimes used in these cases as a cheaper alternative to Revatio.

1.3. How common is off-label use?

Because there is no requirement to register off-label prescriptions and the prescribing doctors are not obliged to specify off-label use on the prescriptions they issue, there are no accurate data on the extent of off-label use. The indication, target group, age... which the medicinal product is used for do not need to be disclosed to the National Institute for Health and Disability Insurance (NIHDI) to qualify for reimbursement, unless certificate drugs are prescribed (Chapter IV, IVbis), the reimbursement of which is, for medical and/or budgetary reasons, limited to specific indications, a specific target group, age.... It is common knowledge however that medicines are often prescribed off-label to children, pregnant women and in the fields of oncology, obstetrics, infectious diseases (HIV/aids) and palliative care. It is estimated that up to 80% of the medicinal products used in paediatrics and at least half of those used in oncology are off-label.

[b] If Siklos would be commercialised on the Belgian market, the off-label use of Hydrea shouldn't be supported, since this would undermine the market exclusivity of the orphan drug (see chapter 3).

1.4. Proof of safety and efficacy is often lacking

Unlike in the case of authorised medicinal products, there often is no proof as to the safety and efficacy of off-label use. Information on off-label use is mainly derived from individual patient files (case reports) or from the experiences of individual experts (expert opinion). Furthermore, an authorised medicinal product that is safe and effective for one indication is not necessarily safe and effective when used off-label. In cases like these, we could be dealing with a different indication, age group, additional conditions, co-medication, etc.

The absence of information on the safety and efficacy of off-label use leads to uncertainty and discussion amongst the parties concerned. Doctors in and outside of hospitals take on a great deal of responsibility when prescribing off-label as it could always expose patients to health risks, assuming even that the patients concerned actually know that they are being treated with an off-label used product. The reimbursement of a product that has not been proven to be both safe and effective also seems hard to justify.

Examples of harmful off-label

Mediator as weight reduction pill

In France, Mediator was authorised as a therapy for overweight diabetes patients but it turned out to cause fatal cardiac conditions in these patients. During the period that this side-effect was not yet known, Mediator was also prescribed off-label as a slimming drug with the result that the number of fatal cardiac conditions increased even further.

Antipsychotics in rest homes in elderly people with dementia

The off-label use of antipsychotics in elderly people in rest homes is not innocent and causes an increased mortality.

1.5. In practice, only the MA holder can apply for an MA for a new (now off-label) indication, but often he is not interested.

In principle, **anyone can apply for an MA or an extension** for other indications. When doing so, the quality, safety and efficacy of the product must be demonstrated for the indication(s) concerned. Non-industrial partners regularly request to obtain an MA, but to our knowledge this was never realised in practice.

Thus**, in theory, third parties** (university researchers, public institutions, patient organisations and non-profit organisations) **could also apply for an MA but, in practice, that is often easier said than done**. Preparing the file is a highly time-consuming and expensive affair. Aside from the fact that interested third parties will more often than not have to cover the cost of the drugs used in the study themselves, they will also need to describe the production process and supply the non-clinical data, and, unless the MA holder is prepared to disclose these data, it is impossible for third parties to get their hands on them. Getting insurance cover for clinical trials can prove to be another challenge, especially if the MA holder is unwilling to back the project. At that, there is no certainty that the MA holder will actually be prepared to supply the drug (and the corresponding placebo) once a MA has been obtained.

Often, pharmaceutical companies do not have a whole lot to gain, be it financially or legally, from extending the MA for a medicinal product that is authorised already to new indications or modalities. When they do, they are obliged to invest in additional clinical research even though the drug is being used off-label as it is and they are generating revenue from that off-label use also.

An extension of the indications sometimes results in a **global price reduction of the medicinal product,** based on the argument that an extension of the indications is sure to boost turnover.

In addition, the indications in question are often rare or in children, with the result that the **market is limited** and that there is no cast-iron guarantee that they will ever recoup their investment. Additional studies can also bring **safety issues or a lower efficacy** to light which could reduce sales of the product.

Finally, the current **legislation on patents and data exclusivity** especially favours the development of new products and not the use of existing products for new indications or modalities. The business model of the pharmaceutical companies has also been designed around that. As a consequence, companies often stop testing for new indications long before the patent of a medicinal product is due to expire. The clinical trials required for a new condition take years and time is often no longer on the MA holders' side when it comes to recouping this investment. For older drugs which have come off patent there is no incentive to register new applications because all the applications of the original medicinal product can also be included in the label of its generic competitors.

1.6. Research questions

The current report aims to answer the following research questions:

- What powers do Member States have under EU law to regulate off-label use and under what conditions?
- Can off-label use be regulated (to in-label) via a new MA or via a variation/extension of an existing MA?
- How can the relevant evidence on the safety and efficacy of medicinal products used off-label be generated?

1.7. Methodology

We examined the European and Belgian legislation, including the legislation prevailing within a number of other European and non-European countries. In addition, we examined how the courts of the various countries apply the legislation and whether their case law is compatible with that of the Court of Justice of the European Union. On the basis thereof, we give an overview of the various ways to regulate off-label use in Belgium.

2. EUROPEAN LEGISLATION AND CASE LAW ON OFF-LABEL USE

The protection of citizens' health is one of the underlying principles EU legislation is based on and takes centre stage in the European legislation. As a result, the EU and its Member States can take measures that restrict the important EU principle of free movement of goods (in this instance medicinal products), services and persons. One of these measures is that applicants must apply for marketing authorisation before they can freely sell their medicinal products on the European market. This ensures that the product is properly tested on quality, safety and efficacy before it is released.

2.1. MA is the general rule but off-label use is not forbidden

As a rule, a MA application must be submitted for each use of a medicinal product. **However, Directive 2001/83/EC (hereinafter Pharmaceuticals Directive) and Regulation (EC) No 726/2004 provide for a number of exceptions to this obligation which give the Member States the option to allow the use of unauthorised or the unlicensed use of medicinal products:**

- Medicinal product prepared in a pharmacy (magistral formulas) (Art. 3(1) and (2) of Directive 2001/83/EC);
- Medicinal products intended for approved clinical trials (Art. 3(3) of Directive 2001/83/EC);
- Medicinal products in cases of "medical need", i.e.
  - Special needs (Art. 5(1) of Directive 2001/83/EC): if an individual patient has a special need for (the use of) a medicinal product, the individual doctor can prescribe an unlicensed medicinal product or the off-label use of an authorised medicinal product under his own responsibility.
  - Emergency situations (suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation) (Art. 5(2) and (3) of Directive 2001/83/EC);
  - Compassionate use in cases where no other therapy is available (Art. 83 of Regulation (EC) No 726/2004).

Off-label use comes within the scope of a number of these exceptions.

2.2. Increased focus on off-label use in European pharmacovigilance rules

Even though off-label use is only indirectly referred to under EU legislation as a possible exception to the MA obligation, it is gaining increasing attention in the European pharmacovigilance rules.

For one, MA holders must provide information about the (possible) **side effects** of both the authorised and the off-label use of a medicinal product.

Patients as well can report side effects of off-label used products.

In addition, the competent authorities, who decide on the MA, can also demand that MA holders perform a **post-authorisation study** to confirm the safety of the off-label use of their medicinal product.

MA holders must also notify the competent authorities of any **new information** that can influence the risk-benefit assessment of the authorised and the off-label use of a medicinal product.

2.3. Measures to encourage the extension of existing MAs and research into other uses of medicinal products that have been approved already

As mentioned above (see 1.5), often MA holders are not inclined to apply for an MA for off-label use. To remedy that, a number of measures were taken at European level to entice manufacturers to apply for extension of existing MAs and to encourage further research into the safety and efficacy of authorised medicinal products for other indications or target groups.

A distinction is made between MA extensions and variations, which are subject to different procedures (and varying degrees of strictness).[c] Variations include changes to the MA dossier, from a modification in the product's name to invasive changes having a major impact on the quality, safety or efficacy, such as adding new therapeutic indications. Extensions are fundamental changes (other than these considered as variations) to elements of the MA of a pharmaceutical, such as changes in the active substance, pharmaceutical form, dose or route of administration. Variation or extension procedures tend to be **less stringent and less expensive** than for an initial MA.

In addition, **one extra year market protection** (in the form of data exclusivity) can be granted when authorisation for a new indication was obtained.

An extension of one year data exclusivity is granted if, during the first eight years of the ten year market protection[d], the MA holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies (art. 10(1) Pharmaceuticals Directive). This extra year can be very valuable as it not only covers the new indication, but the entire product. Moreover, this can be very valuable if the medicinal product is no longer effectively covered by the patent.

Where an application is made for a new indication for a well-established substance, a period of one year of data exclusivity is granted for the new indication, provided significant pre-clinical or clinical studies were carried out in relation to the new indication (art. 10(5) Pharmaceuticals Directive). One extra year market protection after an MA is too short a period to allow manufacturers to recoup their investment in research into a new indication of older medicinal products, especially in small populations like children or patients suffering from rare diseases. Moreover, it only covers the new indication.

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cc There are several types of variations, ranging from less invasive to invasive (IA, IB, II). The Variations Regulation and the related guideline list the changes that are to be considered as type II variations (most fundamental changes). De modifications that are considered to be extensions are listed in annex I of the Variations Regulation. See for more information: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000104.jsp&mid=WC0b01ac0580025b88

d An authorised generic medicinal product may not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.

Yet, extending market protection any further could be dangerous as this would enable MA holders to keep generics off the market by repeatedly reapplying for an extension or a variation of the MA.

Another reason why the above measures do not seem to produce the desired result is that, in practice, off-label use is already widespread. Since MA holders generate income from off-label use anyhow, there is no financial incentive to invest in further research.

Aside from the options of MA variation or extension, there is also legislation that aims to support research and development of medicinal products for rare diseases and children (see the Scientific Report, section 3.3.2). These measures have a positive impact on the availability of authorised (paediatric) pharmaceuticals. Yet, substantive off-label use remains a reality (see references scientific report 1.1. and 3.3.2.3.).

3. WHAT LEEWAY DOES EUROPE GIVE ITS MEMBER STATES TO SUPPORT RESPONSIBLE OFF-LABEL USE?

3.1. Balance between protecting public health and corporate interests

The EU has the powers to guarantee the **free movement of medicinal products and fair competition** within the pharmaceutical sector. As set out above, specific EU legislation, mainly to harmonise market access of qualitative and safe medicinal products, has been put in place.

In addition, principles of European law put the protection of citizens' health centre stage. This is why MA holders are obliged to apply for an MA if they want to bring a medicinal product onto the market. But Directive 2001/83/EC and Regulation (EC) No 726/2004 provide for a number of exceptions which should be interpreted restrictively.[3] Off-label use could be deemed to be one such exception.

Other than the EU, also the Member States are vested with the powers to protect **the health of their citizens**. After all, it is their responsibility to outline national health policy and to organise and provide health services and medical care. They also have complete autonomy when it comes to deciding where their resources are spent. Possible measures within the framework of national healthcare policies could be the reimbursement of certain medicines, the dissemination of information or the promotion of the use of certain medicinal products.

EU legislation and doctrine aim to create a balance between the protection of public health on the one hand, and the economic interests of the corporate sector, on the other hand. Member States are free to introduce policy measures on off-label use provided they do not undermine the European legislative framework on medicinal products. As they are bound by an obligation of sincere cooperation, they must do everything in their power to fulfil the obligations ensuing from the Treaty and must refrain from taking any measures that can hamper the proper functioning of the European Union.

So far, the European Commission has **not taken a clear stance yet** on what room for manoeuver the Member States have when it comes to supporting off-label use. In a Resolution of the European Parliament on patient safety[4], the EMA was encouraged to set a list of off-label used pharmaceuticals with an authorised alternative and to draft guidelines on the off-label use. The European Commission states that although the EMA could play an important role, setting a list would possibly not be representative as not all member states have the same authorised products on their market. Moreover some countries have their own recommendations on off-label use. Even the Court of Justice of the European Union has not made any explicit ruling on the policy of some Member States to support and reimburse off-label use, even when an authorised alternative is available.

3.2. Stimulating off-label use solely for financial reasons does not conform to EU legislation but reimbursement in individual cases does

Although there is no jurisprudence of the European Court of Justice on the lawfulness of a national policy supporting and reimbursing off-label use (such as for instance in France), a number of principles can be deduced from existing relevant jurisprudence. It always concerns, however, rulings of the Court in particular cases and specific circumstances. As such, they cannot be straightforwardly be applied to the specific situation of a national authority supporting and reimbursing off-label use.

Under European legislation, the **commercial promotion[e] of medicinal products for indications they have not been licensed for is not permitted**. However, the Court of Justice of the European Union found that the healthcare policy of a Member State is not commercially motivated. For that reason, a financial incentive within a policy of this nature, such as the reimbursement of a medicinal product, **cannot be regarded as commercial promotion**. The same applies to the dissemination of information on medicinal products by a national authority.

However, the fact that the non-commercial promotion of off-label use by a Member State is not illegal in principle **is not a justifiable motive to actually support off-label use**. As stated earlier, policy measures must not undermine the European (pharmaceutical) legislation. The financial results of manufacturers of authorised medicinal products can be seriously affected by a policy on off-label use. The pharmaceutical industry invests in research and the development of innovative and safe medicinal products. This fact is taken into account by the existing system of granting MAs, which is based on a balance between protection of public health and the protection of the interests of the industry. This system of granting MAs would be undermined if authorities would decide to promote and reimburse off-label use solely for budgetary reasons.

From case law of the Court of Justice of the European Union (see chapter 3.4. of the Scientific Report) it can also be deduced **that Member States are not at liberty to encourage or reimburse off-label use purely on the basis that it would be financially more beneficial for health insurance providers**.[5]

On an earlier occasion however, the Court of Justice did rule that measures that steer the use of certain medicinal products to ensure the financial stability of the social security system or the integrity of the healthcare system on a wider scale can be justified. Measures like these should only be taken with public health in mind and should not adversely affect the effectiveness of the principles of the MAs and related rights.

Furthermore, a judgment of 11 June 2015 set out a number of important principles with regard to **the indirect promotion of off-label use.**[6] The Court decided that the provisions on safety and efficacy of (for the authorised indications irrelevant) off-label indications in the summary of the product characteristics of the medicinal product and in the assessment report undermined the market exclusivity of the rival (orphan) drug. The conclusions on the safety and efficacy of the non-authorised indications did not contribute to a better knowledge of the pharmaceutical in the authorised indication, but was an indirect promotion of an off-label indication. As market exclusivity is the main driver for orphan drugs, this indirect promotion was inconsistent with the objectives of EU law.

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[e] This means that the use of the medicinal product other than for the authorised indication is encouraged, for instance organisation of training sessions, consultants recommending off-label use to physicians or pharmacists, financing research and grants for marketing purposes.

The judgment also confirmed that doctors only, based on patient-specific therapeutic considerations, are responsible for the prescription of off-label use. The extent of this responsibility can be influenced by statements in the summary of the product characteristics and the assessment report which state that off-label use is safe and effective. As such, in this case the statements in the respective documents were judged to be unlawful.

This leads us to conclude that the **promotion of off-label use** for cost reasons is not in conformity with current European legislation. **Member States are free, however, to reimburse** off-label use in cases where the doctor decides that this is the best option for the patient in question. **Member States can also provide information** on off-label use to physicians, provided they do not interfere with doctors' discretionary powers and autonomy. In that light, **the provision of evidence of off-label use** does seem **justified**.

Based on these findings, a step-by-step plan was developed which could be used for a national policy on off-label use (see below).

4. LIABILITY IN CASES OF OFF-LABEL USE

As mentioned, off-label use is not banned under European legislation. Yet, in certain cases, the parties listed hereafter may be held liable for any damage that may be sustained as a result.

4.1. Product liability on the part of producers

EU legislation stipulates that the producer is liable for damage caused by a defect in his product without negligence on his part having to be established.[7] The manufacturer is liable for the negative effects of a medicinal product in the authorised indication he failed to warn about and which manifest themselves in spite of the product having been used in line with the directions on the leaflet (on-label).

It is unlikely though that a manufacturer would be held liable for any harm a patient may have sustained as a result of off-label use if the patient was duly informed by his doctor and by the leaflet about the possible risks and if the harm was not caused by an inherent defect to the product or an error/omission in the leaflet. The risk of liability does increase if the manufacturer was aware or should have been aware of the harmful effects of the off-label use of his product and/or if he actively promoted it (which is unlawful). As a consequence of the increased focus on off-label use in the pharmacovigilance rules (see 2.2), off-label use is deemed to be foreseeable by the manufacturer.

To contain the risk of liability inasmuch as possible, it is in the manufacturers' own interest to follow up the quality and safety of their medicinal products and to include warnings about the possible side effects and contraindications of (off-label) use of their medicinal products in their leaflets.

4.2. Liability on the part of the prescribing doctor

In line with the principle of therapeutic freedom, doctors can prescribe medicinal products off-label, but that does not exempt them from civil liability if the patient suffers harm as a result. Their liability for harm sustained as a result of off-label use must be assessed on a case-by-case basis and, when doing so, the courts will examine what a prudent and reasonable doctor would have done in the same circumstances. In their assessment, the judges will base themselves on three criteria:

- *What is standard practice and does the off-label prescription of the medicinal product tie in with that?*

  As we pointed out earlier, prescribing medicines off-label is a widespread medical practice, especially if there is no alternative, authorised therapy to hand. Where there is an alternative however, chances that the doctor will be held liable will also increase. In situations like these, he/she will have to demonstrate that the medicinal product prescribed off-label is the standard therapy in practice or that the off-label therapy was the best one for the patient concerned (for instance because the patient was unable to tolerate the authorised product).

- *Are there scientific grounds for the off-label use?*

  Where a doctor based himself on scientifically sound clinical practice guidelines or on scientific literature he will be deemed to have acted prudently and carefully.

- *Informed consent*

  The court will also examine whether the patient gave his informed consent before the therapy was started.[f] That consent must be explicit. Thus, it is essential that doctors also clarify to their patients that the medicinal product they are proposing is being used off-label and that they explain the possible risks of such off-label use. If no or very little clinical research was done into this specific use, the patient should be told. On the other hand, and on the basis of these principles, a decision NOT to prescribe a medicinal product off-label can in certain circumstances also be construed as negligence on the part of the doctor.

If a doctor is held liable for physical harm to a patient as a result of an unwarranted off-label prescription, he/she may also face criminal and disciplinary action.

4.3. Liability of pharmacists and the Medico-Pharmaceutical Committee

Pharmacists can be held liable for damage caused by a defective magistral formula. They are responsible for the quality of the magistral formula: correct weighing, right products, product imperfections… Where preparations are used in unusual circumstances or for indications that have not been studied in clinical trials and/or have not been validated by an MA, pharmacists must be doubly careful.

Pharmacists must also analyse the prescription based on the pharmacological aspects, indications, interactions, possible side effects and other drug-related problems.[8] And they must check whether the products are the most appropriate for the patient in question, without detracting from the therapeutic freedom of the doctor. In other words, pharmacists must properly inform their customers about the off-label use of a medicinal product. But, often, pharmacists are not aware of indication and thus the off-label use of a medicinal product they dispense. They can check the off-label use if it relates to the patient group (children, pregnant women…), dose and route of administration, but not the indication. In that sense, the risk of liability for the failure to advise customers on an off-label use which they could not have been aware of is fairly slim.

The Medico-Pharmaceutical Committee (MFC) is a statutory hospital body that determines which medicinal products doctors are allowed to prescribe in hospital. These medicinal products are listed in the Therapeutic Formulary. In line with their therapeutic freedom, doctors may deviate from the guidelines of the MFC. What's more, if they are of the opinion that off-label use for a certain patient is not the best or even a harmful therapeutic

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[f] In an advice of 5 September 2009, the National Order of Physicians stated that the patient needs to be carefully informed: *"According to art. 7 § 2 of the Patients' Rights Act of 22 August 2002, the physician needs to inform the patient orally and/or in written, in a clear language on all necessary information regarding the therapeutic indication justifying the prescription*".

option they are in fact obliged to deviate from the MFC guidelines. However, the alternatives a doctor may wish to prescribe may not always be available on a permanent basis in the hospital pharmacy.

The regulations stipulate that the formulary must be compiled in a considered and economically justifiable manner.[9] They do not state however that an MFC must abide by the information in the leaflet for instance. There is room for discussion on the inclusion of similar medicinal products with a partially overlapping list of indications in the formulary. For one, this would be the case already for a number of low molecular weight heparins (a class of anticoagulant medication). Only Clexane also has the indication "bedridden patients" (without surgery). As such, hospitals are reluctant to select Fragmin as sole fragmented heparin for the formulary. This means that if the MFC wants to list all the possible indications in the formulary on-label, often several products will have to be included, which may not tie in with the hospital administrator's idea of an optimum policy.

By virtue of its general duty of care, the MFC must base its decisions on the scientific knowledge on a medicinal product that is available. Hence, the inclusion of certain medicinal products in the formulary purely for budgetary considerations seems hard to justify. As mentioned earlier, the final responsibility for prescribing a medicinal product does rest with the doctor. It is up to a judge to rule on the respective liabilities of the parties concerned (physician, the MFC, the hospital, etc.) on a case-by-case basis.[g]

4.4. Liability on the part of the authorities

National authorities have a general obligation to protect and promote public health. They can take policy measures on off-label use provided they do not undermine the European legislative framework on medicinal products. This for one boils down to the fact that they are not allowed to interfere with the effectiveness of the MA and the rights associated with it. Prescribing off-label use comes within the remit of the individual doctors and policy measures should not interfere with that. If an authority promotes off-label use on cost-saving grounds, it may be held liable.

In that case, it will be examined whether a normally prudent authority, given the same circumstances, would have acted in the same manner. Other European authorities such as France, Hungary and Italy already decided to consider off-label use for financing on economic grounds even in cases where an authorised alternative is available (see frame under 6). So far, there has been no verdict on whether these decisions are in compliance with EU law.

[g] The legal relationships between parties (who did the patient contract with?, What is the legal relationship between the hospital and the physician,…) determines who will bear liability

5. BELGIAN LEGISLATION ON OFF-LABEL USE

5.1. How is off-label use regulated in Belgium at present?

5.1.1. Medicines Act

Article 6 of the Belgian Medicines Act lists a number of cases where medicinal products may be used without MA or contrary to the terms of their MA. Even though most of the provisions are a transposition of the European legislation, the Belgian legislation does offer a wider framework.

1. Special needs (art. 6 quater, 1°)

The patient has a special need that, other than with the (unlicensed) product, cannot be properly treated with the medicinal products authorised in Belgium. In situations like these, the legislator can decide that the medicinal product in question can be used for one single patient or for a group of patients under the direct personal responsibility of the doctor, which ties in with the principle of the therapeutic freedom of doctors.

2. Compassionate use (art. 6 quater, §1, 2°):

For patients suffering from a chronic illness or from an illness that severely affects their quality of life or from a life-threatening condition that cannot be successfully treated with an authorised medicinal product, the authorities can **authorise the use of medicinal products without MA, of unlicensed products in other words**, provided an MA application has been submitted for the product concerned or clinical research into the indication in question is being conducted.

3. Medical need programme (art. 6 quater, §1, 3°):

In this case, the product **DID obtain an MA, though NOT** for the treatment of a specific chronic illness, a seriously debilitating disease or a life-threatening condition that cannot be successfully treated with a product that is authorised for this particular indication and is commercially available in Belgium. This relates to the off-label use of an authorised product in other words.

The authority can sanction this use provided at least one of the following additional conditions have been fulfilled:

- an application for an MA for the indication is question has been filed OR
- the MA for the indication has been obtained but the product is not commercially available OR
- clinical research into this indication is ongoing or clinical trials have been conducted that demonstrate that the medicinal product in question is a suitable therapy for the condition concerned.

4. Imports from another Member State for an individual patient (art. 6 quater §1, 4°)

The Act provides that, for an individual patient, permission can be granted to import an unlicensed product from another Member State where the product has been authorised (parallel import). Prerequisite is however that there is no suitable authorised product available in Belgium or that such product is temporarily or permanently unavailable.

5. Serious threat to public health (art. 6 quater, §1, 5°)

The Minister for Public Health can also authorise the distribution of unlicensed products in cases where there is a serious threat to public health.

6. No MA required for lack of relevance (art. 6 quater §3)

This applies to products that are not mass-produced (e.g. plasma, blood, magistral formulas) or in cases where alternative safety and authorisation procedures prevail (e.g. products used in medical experiments).

5.1.2. Therapeutic freedom of doctors to prescribe off-label

The authority to prescribe off-label forms part of the therapeutic freedom of doctors. Prerequisite here however is that the doctor obtains the patient's informed consent and that the off-label therapy with the medicinal product concerned is scientifically underpinned. After all, if the patient suffers harm as a result of the off-label use, the doctor can be held liable, as discussed in section 4.2. On the other hand, a doctor may be guilty of medical negligence if he does not use a vital drug, even in an off-label indication.

Many doctors prescribe off-label but are not fully au fait with these obligations and risks. Information campaigns organised by the authorities could redress that situation (see section 7.1 and recommendations)

5.1.3. *Freedom of researchers to conduct studies on the off-label use of medicinal products*

Researchers are entitled to study the off-label use of medicinal products provided they abide by the legislation on medical experiments[10]. Here too, the informed consent of the patients concerned is crucial. What's more, clinical trials cannot start unless prior permission has been obtained from a Medical Ethics Commission and provided the competent authority (FAMHP) did not report any objections within the statutory timeframe laid down by the Law concerning Experiments on the Human Person. As mentioned in section 1.5 above, it is often very difficult for researchers-sponsors to obtain an MA for off-label use without the producer's support.

5.1.4. *Promotion of off-label use by MA holders is forbidden*

The commercial promotion of medicinal products for off-label use by MA holders, such as the organisation of training sessions, sales representatives recommending off-label use to doctors and pharmacists, the funding of research and study grants for marketing purposes, is not permitted (art. 9 § 1 Act on Pharmaceuticals[11]). Purely scientific results can be discussed however if this is not done with a view to encouraging the sale or prescription of the respective medicinal product in question.

5.2. Reimbursement of off-label use in Belgium

5.2.1. *Unmet medical need programme*

Since 2014,[12] any pharmaceutical company, the Minister for Social Affairs or Public Health or the College of Medical Directors can, for a cohort of patients ask for financial support for certain innovative medicinal products, even before they are authorised. This new procedure goes by the name of "Unmet Medical Need" and fast-tracks access to innovative medicinal products. On the basis of the application, the College of Medical Directors will decide on a cohort whereupon an application can be filed for each patient individually. If the individual decision is positive, the patient won't pay anything for the medicinal product.

To qualify, the following cumulative conditions must be met:

1. The medicinal product is designed to treat a **serious or life-threatening condition**; AND
2. There is **no acceptable alternative therapy** that is refunded by the compulsory health insurance ('therapy' in this instance refers to all kinds of therapies, and not exclusively to drug therapies); AND
3. The medicinal product is used as a **compassionate use** therapy or within the framework of **a medical need programme (see 5.1.1)**; AND
4. The medicinal product in question is used for a condition that features on the list of unmet medical needs.[h] If it was not possible to timely submit a request to be included in the list, a pharmaceutical can be taken into consideration for a cohort decision anyway if the General Council agreed following an advice of the "Commission for advice for temporary financing of pharmaceuticals" and the College of physicians-directors.

Because this measure was introduced only very recently, it is too early to assess its impact at this moment in time (July 2015). The recent pact on the future for patients with the pharmaceutical industry (hereinafter the medicinal products pact) does specify however that the unmet medical need programme will be evaluated at the end of 2016. In function of the results, the procedure and budget will be adjusted. So far, a number of barriers have been identified however.

Even though, aside from the manufacturer, also the College of Medical Directors and the Minister for Social Affairs or Public Health have the authority to submit a cohort application, the collaboration of the pharmaceutical company remains a requirement. After all, the medicinal product must form part of a compassionate use programme or be used within a medical need programme to begin with. As a minimum, that will require the manufacturer's cooperation as he needs to supply the product, the production process data, etc. Moreover, manufacturers can always take

[h] Firms or the Minister of Social Affairs or Public Health can submit a request to be enrolled to the list until the 15th of May of each year. On the 31st of October of the same year the General Council sets a definitive list for the next year. The advices of the "Commission for advice in case of temporary financing the use of a pharmaceutical" and the College of Physicians-Directors are taken into account. The economic and medical impact plays a role as well. At the moment of the writing of the report, no list was set yet.

the initiative to put an end to a compassionate use or medical need programme.

Manufacturers may have several reasons not to take part in a compassionate use or medical need programme. If far higher doses are required for the new indication than for the one the MA was obtained, manufacturers may be slow to enter the medical need programme for the new indication. After all, there is always a risk that the price of the medicinal product will come under pressure if it turns out that the therapeutic added value of the medicine in the new indication is not proportionate to the extra cost relative to the current price.

The undisclosed non-clinical data (a. o. toxicology) a company has at its disposal can be another reason why certain indications are developed further and others not.

Another factor could be that the cost of setting up a programme involving data collection may very well outweigh the manufacturer's possible future gains. Furthermore, compassionate use or medical need programmes also entail responsibilities at pharmacovigilance level. For one, the doctor who submits the compassionate use or medical need application will have to report back to the manufacturer about its efficacy and side effects which can have an impact on the use of the medicinal product.

There are also a number of ambiguities about how the products used in a compassionate use or medical need programme will be reimbursed. So far, there are no details about how reimbursement for these products will be decided. And because there is no effective reimbursable alternative, there is no price comparator either. At that, it is not yet clear whether the price that was fixed in the unmet medical need programme will also have an impact on the price of the product once it has obtained an MA. An evaluation of the existing programmes therefore seems warranted if they are to be optimally applied.

Table 1 – Compassionate use - medical need programme and reimbursement via the unmet medical need programme

Use during early market access	Compassionate use (CU)	Medical Need Programme (MN)
MA?	No **= Use of unlicensed product**	Yes, but for (a) different indication(s) **= Off-label use**
MA application in progress?	Yes or clinical trial taking place	Yes or clinical trial taking place
For whom?	for patients suffering from a chronic illness, a severely debilitating disease or a life-threatening condition that cannot be successfully treated with an authorised medicinal product	for patients suffering from a chronic illness, a severely debilitating disease or a life-threatening condition that cannot be successfully treated with a medicinal product authorised for the indication in question and is commercially available in Belgium
Applicant	Manufacturer or other interested party, the Minister of Public Health or Social Affairs included	Manufacturer or other interested party, the Minister of Public Health or Social Affairs included
Financial support	**Unmet medical need programme**	
Applicant	Manufacturer College of Medical Directors* Minister for Social Affairs or Public Health*	
Conditions	- medicinal product for a serious or life-threatening condition - no acceptable alternative therapy that is reimbursed - medicinal product in CU or MN program; - medicinal product used for a condition that features on the list of unmet medical needs.	

** In practice, the success of the application will hinge on the company's goodwill*

5.2.2. *Individual application by patients to the Special Solidarity Fund*

Individual patients suffering from a very serious condition can also apply to the Special Solidarity Fund (SSF) for financial support for certain types of highly expensive medical care and therapy costs that are not reimbursed. This means that certain cases of off-label use for which there is no suitable reimbursable alternative to hand may qualify for this type of support.

The SSF may be called upon in any one of the following cases[13]:

- The indication for which the therapy was prescribed, is rare.
- Rare condition.
- Rare condition for which the patient requires continuous and complex care.
- Medical devices and/or services qualified as innovative medical techniques to the exclusion of medicinal products.
- Treatment for a seriously chronically ill child.
- Care abroad.

In addition, each one of these categories must satisfy a number of criteria. The main criteria are:

- The therapy is expensive.
- The scientific value and efficacy of the therapy have been properly substantiated and are by and large recognised by the authoritative medical bodies.
- The therapy is prescribed to treat vital functions that are at risk.
- Another therapy that qualifies for reimbursement or for another source of funding is not an option for the patient.
- The therapy has been prescribed by a consultant specialised in the condition in question.

The SSF has a closed budget and fixes the reimbursement basis per individual application at its own discretion. The Fund could intervene in the costs for up to 75 % while the patient bears the remaining 25 % for instance, with the personal contribution being capped at € 1250 per annum. It is not clear however who covers the cost once the patient's own contribution is exceeded. If the discrepancy is not covered by the producer, the physician, the hospital or another party will de facto bear the costs.

This SSF support could discourage manufacturers from taking part in a medical need programme, for, once the SSF has agreed to intervene, manufacturers often have less reason to supply the patient with the product free of charge within the framework of a medical need or compassionate use programme pending a possible contribution via the unmet medical need programme or via the standard reimbursement scheme.

Support by the SSF is not subject to specific requirements in terms of the amount or quality of the evidence either. The experimental stage must have been completed but, due to the nature of the applications (rare, difficult to fit into the regular reimbursement schemes), small series or case reports must be relied on at times. In contrast to the medical need and compassionate use programmes, no clinical trial or an MA application must be in progress. What's more, there is no requirement to generate additional evidence or to follow up the effects of the use of the medicinal product afterwards. In that manner, the SSF can remain on board for years without any evaluation on the use of the medicinal product taking place in the long term.

SSF as waiting room, with reimbursement for off-label use

The use of Nizoral (ketoconaloze) as an antifungal medication was discontinued after severe cases of liver toxicity were reported. However, this molecule in the same dose also seems to inhibit the production of steroids. For that reason, the EMA recognised this molecule as an orphan drug to treat the rare Cushing's Syndrome. There is no speciality on hand for this condition, though ketoconazole now features on the list of authorised ingredients (this is different from the concept "authorised pharmaceutical" as defined in the introduction). Pending reimbursement of a magistral formula containing ketconazole, the SSF is still being used as a kind of waiting room to obtain reimbursement.

5.2.3. Reimbursement via the mandatory health insurance

Aside from financial support within the framework of the unmet medical need programme or the SSF, which is only available for a limited niche of off-label use, off-label use can also be reimbursed via the "regular" reimbursement procedures. In contrast to support via the SSF or the unmet medical need programme, patients may also qualify for reimbursement in cases where an authorised alternative is available.

For reimbursement purposes in Belgium, medicinal products are subdivided into a number of classes (A, B, C, Cs, Cx, D, Fa, Fb) and chapters (I, II, III, IV, IVbis, VII) on the list of reimbursable pharmaceutical specialities.[14] For off-label use context, an example where a shift from chapter IV to chapter I was realised, is elaboration underneath.

Originally, medicinal products in Chapter I could only be reimbursed for the authorised indications listed on the leaflet, but following a 2012 amendment to the legislation, off-label use can now also be refunded. [15]

The reimbursement of a **medicinal product listed in Chapter IV** is governed by conditions that are imposed for medical and/or economic reasons. This entails that reimbursement is limited to e.g. indications, target group, age, dose, prescribers… In addition, usually a prior authorisation of the NIHDI advisory physician is required.[i] Other than for medicinal products in Chapter IV, doctors do not have to specify the indication, target group, age etc. So there is no way of knowing whether the contributions NIHDI pays relate to authorised or off-label use.

Since a 2012 amendment to the legislation, the NIHDI - with the agreement of the manufacturers and subject to a price reduction to neutralise budgetary consequences of increased volumes - has regularly moved medicinal products listed in Chapter IV to Chapter I. The objective was to allow a wider reimbursement than the initially defined indications, target groups, doses, prescribers… (i.e. wider than the reimbursement categories defined for Chapter IV). This indirectly also facilitated the refunding of off-label use.

As it happens, the recent medicinal product pact also contains a statement of intent to register cheap off-patent cancer drugs in Chapter I so that they would be exempt from the "Chapter IV procedures". The idea is that this will allow their use to be monitored and followed up in order to guarantee their medically justified and rational use.

Off-label use in **hospitals** can also qualify for reimbursement. Since 1 July 2006, the acute hospitals have been applying a lump sum reimbursement system per admission for all reimbursable medicinal products, irrespective of their actual use. However, certain products are excluded from this limp sum system such as orphan drugs, cytostatics, immunoglobulins, HIV inhibitors…

Off-label use of medicinal products in hospitals can be reimbursed as follows:

- The medicinal product is reimbursed under Chapter I:
  - The Chapter I rules apply. Since the 2012 legislative amendment, off-label use now qualifies for reimbursement.
- The medicinal product is reimbursed under certain conditions (Chapter IV):
  - If the medicinal product QUALIFIES for the lump sum system, no prior authorisation from the advisory physician is required (save in exceptional cases): the irrevocable assumption prevails that the reimbursement conditions are satisfied and the Chapter I. procedure is followed virtually.
  - If the medicinal product does NOT qualify for the lump sum system, only the applications mentioned in the reimbursement criteria are reimbursed. Proof that a medicinal product was used in line with the NIHDI rules does not have to be forwarded but it must be kept at the NIHDI's disposal. Where an off-label application is prescribed, the patient must cover the cost of the medicinal product if it transpires from the hospital's information/justification to the advisory physician that the reimbursement conditions were not

[i] As a general rule (with exceptions) for the out-patient setting and in particular situations for use at the hospital

met. If the hospital does not notify the advisory physician to that effect, the invoice to the patient can be revoked.

Since 2012, category F offers the health insurance provider the option to refund a fixed amount if there are several, often expensive, medicinal products available a hospital patient can be treated with. For instance, the health insurance provider could reimburse a fixed amount which may be slightly higher than the price of the cheapest (off-label) medicinal product. If patients do end up having to take the more expensive medicinal product, because they are unable to tolerate the cheaper product for instance, the difference between the fixed amount and the higher price cannot be passed on to them. In this example, hospitals can use the revenue they generate from using the cheapest product. An application of this reimbursement mechanism for off-label medicinal products could be fitted in the step-by-step plan (see 7.1).

Cellcept (mycophenolate mofetil): example of transfer from Chapter IV to Chapter I

Cellcept (mycophenolate mofetil) and its generics do not qualify under the lump sum hospital system. Their only indication is to prevent the rejection of a solid organ implant (liver, kidney, heart) and, as such, the medicinal products in question are listed in Chapter IV. Yet, the molecule is also used off-label in bone marrow transplants and is currently being tested in a range of auto-immune disorders. While CellCept was listed in Chapter IV, the College (SSF) often received applications for off-label indications. Since the product was transferred to Chapter I, no more applications have been submitted to the SSF.

6. LEGISLATION ON OFF-LABEL USE ABROAD

In our scientific report (Chapter 4) we describe the legislation on the off-label use of medicinal products in France, Italy, Hungary, Spain, Austria, Germany, the United Kingdom, the Netherlands, China and the United States.

Even though off-label use is widespread, there is **no uniform policy** and each country operates its own standards. Aside from having implemented the European legislation (see 2.1), some countries also introduced additional legislation. In the Netherlands for instance, off-label use by an individual doctor is permitted by law, though under certain conditions. The use of the medicinal product for the purpose (e.g. indication/target group) must be recommended in guidelines or protocols. If these are still in the development stage, the prescriber must confer with the pharmacist. In addition, the patient must be correctly informed and consent to the off-label use.

Other countries, such as the United Kingdom, refer to doctors' use of clinical practice guidelines and scientific evidence reports that (scientifically) support or recommend off-label use. Some countries have introduced reimbursement systems for scientifically justified off-label use, usually in cases where there is no authorised alternative is available. Some countries, amongst whom France and Italy, also reimburse off-label use even if there is an authorised alternative.

However, these amount to nothing more than ad hoc solutions which were introduced into the legislation in the wake of the Lucentis/Avastin case (see frame). Their conformity with EU legislation still remains to be confirmed. In none of the studied foreign legislations, commercial promotion of off-label use is allowed. However, all countries **demand that off-label use is scientifically substantiated** and that **patients are properly informed**.

Off-label use of Avastin (bevacizumab) for financial reasons

Avastin (bevacizumab) and Lucentis (ranibizumab) are medicinal products used to treat wet, age-related macular degeneration (AMD), an eye condition that can lead to sight loss.

Avastin was the first of the two products to come onto the market, as a cancer drug originally. Lucentis was specifically developed for the treatment of AMD. Lucentis can easily be injected into the eye, while Avastin needs to be diluted in ampoules first. British and American studies, funded by the authorities, established that this off-label use of Avastin is as effective as Lucentis in the treatment of AMD. A recently published retrospective study based on invoice data in the USA found no difference of infection problems (endophthalmitis) in both products.[16]

Problem is that the price of a dose of Lucentis for the treatment of AMD is far higher than the price of Avastin. In Belgium for instance, an injection of Lucentis costs the health insurance provider more than € 800. It won't come as much of a surprise so that, for budgetary reasons, some Member States give preference to the off-label use of Avastin.

For Belgian patients however Avastin is more expensive (40 €) because it concerns off-label use, which is not reimbursed.

In spite of the repeated requests of European politicians, the manufacturer always refused to apply for an MA for AMD. Meanwhile, France and Italy decided to reimburse the off-label use of Avastin in controlled conditions. However, most of the competent authorities of the other Member States do not permit the off-label use of Avastin for the following reasons:

- Negative risk-benefit ratio (mainly for safety reasons more so than for reasons of efficacy)
- The intravenous application was not developed for the eye and the scientific foundation of this formulation (including the stability and use in the appropriate primary packaging…) is lacking.
- The authorities that allow the use of Avastin for the treatment of AMD are fearing for liability claims

The pharmaceutical industry fought the decision of France and Italy at European Commission level on the basis that it contravenes EU legislation.

In turn, a number of European consumer organisations (amongst which the Belgian Test-Aankoop) accused manufacturers Roche and Novartis of cartelisation. The organisations alleged that the companies in question were trying to prevent the use of the cheaper Avastin to maximise their own profits. For now, the verdict of the European Commission must be awaited. An assessment of all the relevant elements in this dossier, such as safety, efficacy and cost-effectiveness will be necessary to determine which steps the parties involved in this file can take (see step-by-step plan).

7. POSSIBLE MEASURES FOR AN ENHANCED AND RESPONSIBLE OFF-LABEL USE IN BELGIUM

In contrast to the use of medicinal products within an authorised application, there is not always scientific proof of efficacy or patient safety in cases of off-label use. That having been said, there is no denying that off-label use is widespread, especially when there is no alternative available. The current initiatives at European level to regulate off-label use and the measures to stimulate research into off-label use do not always seem to produce the desired results (see 2.3).

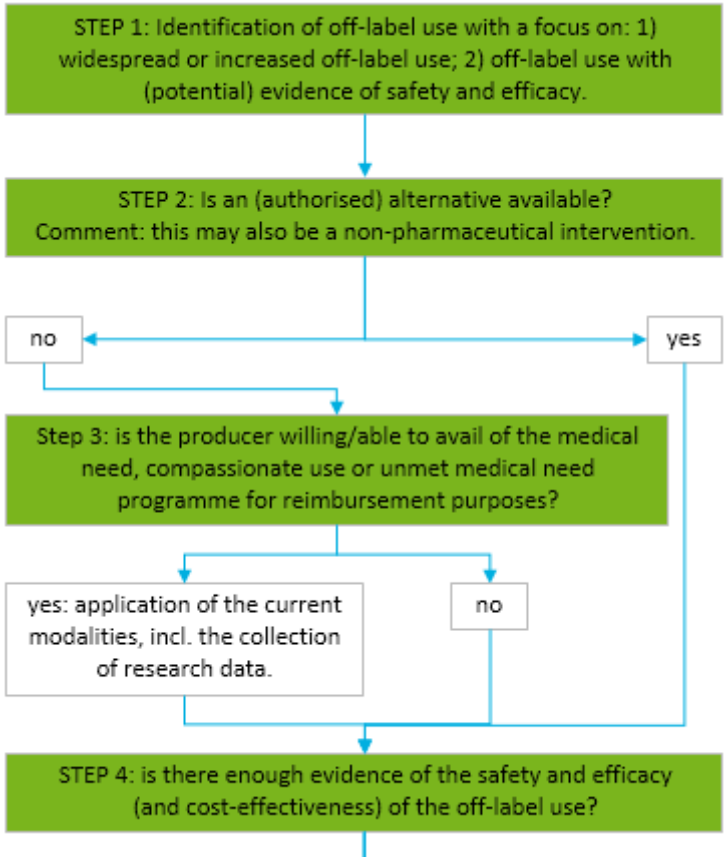
But that does not prevent that a number of measures could be taken at national level to ensure a better and responsible off-label use of medicinal products, with as main objective the protection of patients' health.

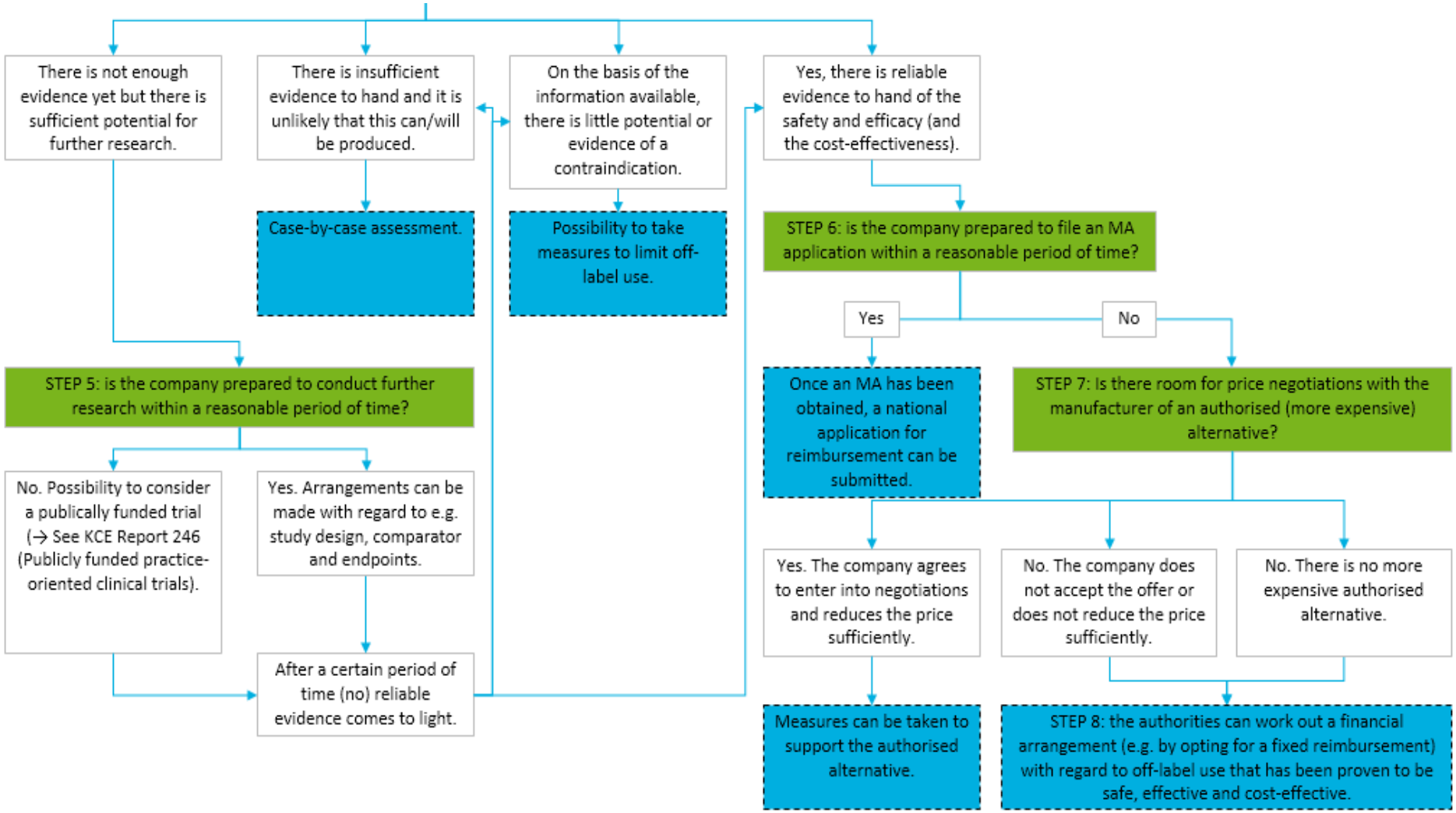
7.1. Step-by-step plan to evaluate widespread off-label use or off-label use with potential evidence of safety and efficacy

The step-by-step plan KCE proposes hereafter could help policy-makers in the healthcare sector to assess and/or generate scientific evidence to ensure the safe, effective and targeted off-label use of medicinal products.

The plan begins by identifying **widespread off-label use or off-label use with potential evidence of safety and efficacy** up to and including the provision of financial support. It also factors in the availability or non-availability of an alternative and of evidence of the safety, efficacy and cost-effectiveness.

It does not provide a conclusive answer to all individual cases of off-label use because the (incidence) of off-label use is often context-specific. There is no such thing as 'the' off-label use in fact. The step-by-step plan merely suggests a number of avenues that could be used within the existing systems. Even though the schedule was developed for the Belgian situation, it can, in the main, also be used in other countries and at European level.




There is not enough evidence yet but there is sufficient potential for further research.
There is insufficient evidence to hand and it is unlikely that this can/will be produced.
On the basis of the information available, there is little potential or evidence of a contraindication.
Yes, there is reliable evidence to hand of the safety and efficacy (and the cost-effectiveness).
Case-by-case assessment.
Possibility to take measures to limit off-label use.
STEP 6: is the company prepared to file an MA application within a reasonable period of time?
Yes
No
STEP 5: is the company prepared to conduct further research within a reasonable period of time?
Once an MA has been obtained, a national application for reimbursement can be submitted.
STEP 7: Is there room for price negotiations with the manufacturer of an authorised (more expensive) alternative?
No. Possibility to consider a publically funded trial (→ See KCE Report 246 (Publicly funded practice-oriented clinical trials).
Yes. Arrangements can be made with regard to e.g. study design, comparator and endpoints.
Yes. The company agrees to enter into negotiations and reduces the price sufficiently.
No. The company does not accept the offer or does not reduce the price sufficiently.
No. There is no more expensive authorised alternative.
After a certain period of time (no) reliable evidence comes to light.
Measures can be taken to support the authorised alternative.
STEP 8: the authorities can work out a financial arrangement (e.g. by opting for a fixed reimbursement) with regard to off-label use that has been proven to be safe, effective and cost-effective.

Step 1: identification of off-label use

The step-by-step plan starts by identifying off-label use. Not all off-label use of medicinal products can be assessed. The focus here lies on the widespread or increased off-label use of medicinal products or off-label use within the indications for which evidence in support may be available. This can be established in several ways:

- **Targeted research into widespread or increased off-label use**:

  The authorities could conduct targeted research into the prevalence of certain off-label use amongst doctors or patients. This was already done in the Netherlands at the instruction of the Healthcare Inspectorate (Inspectie voor de Gezondheidszorg - IGZ).[17]

- **Reporting off-label use with potential evidence of safety and efficacy:**
  Each interested party could report evidence-based off-label use to the authorities (FAMHP/NIHDI). This group of interested parties is extremely broad: the FAMHP or NIHDI itself, the health insurance providers, KCE, the BCFI (Belgian Centre for Pharmacotherapeutic Information), researchers, doctors, hospitals, Test-Aankoop, patients, etc. A certain body could then be asked to examine the safety and efficacy and, if desired, the cost-effectiveness of the off-label use (see hereafter under step 4).

Step 2: is an (authorised) alternative available?

Off-label use is often prevalent in cases where no authorised medicinal product is available. With these situations in mind, a number of modalities have been elaborated in Belgium (see step 3). These can also be resorted to if the only alternative is another off-label use. If there is an authorised and reimbursable medicinal product available however, these modalities will not apply and step 4 can be proceeded to.

Step 3: is the Medical Need, Compassionate Use or Unmet Medical Need Programme an option?

The off-label use of a medicinal product for a condition for which there is no authorised medicinal product available can be authorised in the pre-commercialisation stage via a compassionate use or medical need programme, and may be reimbursed via the unmet medical need programme.
As mentioned earlier (section 3.1.1), manufacturers must be willing to file an application for this or at least be prepared to lend their cooperation. Besides, manufactures can put a stop to a medical need or compassionate use programme at any time.
In cases where an application for a compassionate use or medical need programme is submitted, it is essential that the authorities defines the data collection terms to ensure that they also obtain the data they are particularly interested in. Currently, applicants are asked to supply data in the same format as required for an MA file. The risk-benefit assessment is also performed in the same mind set as for MA applications or clinical trials.

If the authorities are not satisfied with the information that has been collected, they could also decide to assess the existing evidence (step 4) and, where necessary, to generate additional evidence (step 5).

If the aforementioned programmes cannot be resorted to because there is no uptake or because the programme was discontinued early, the authorities (FAMHP/NIHDI) will need to decide within a reasonable period of time whether the safety and efficacy (and the cost-effectiveness) should be assessed (step 4).

Step 4: is there enough evidence as to safety and efficacy?

As the safety and efficacy of off-label use take centre stage, it is also essential that these elements are evaluated. In the short term, that could be done on the basis of the evidence that is available already. In the longer term, research data collected within the framework of one of the above modalities (see step 3) could be used. The medical aspects can be evaluated at European (EMA), particularly for very rare diseases, and at national level (FAMHP, NIHDI, KCE, others…). Currently, applicants have the possibility to request from the FAMHP scientific and/or technical advice[18]related to the research and development aspects of human drug products in view of potential clinical trial applications, MA's, introduction of variations to marketed drug products or line extensions[j]. Experts in specific domains can be invited for this advice. The advice procedure could be extended for the evaluation of off-label used products. The evaluation of quality needs to take place centrally at the FAMHP as the necessary data for this evaluation are not always publicly available.

For innovative (off-label) therapies in oncology an advising expert committee gains in importance because of the rapid and complex evolutions in the domain. In oncology many new pharmaceuticals are specifically targeted to molecular characteristics of a tumour. Some of these targeted pharmaceuticals are already reimbursed by the compulsory health insurance.[19] The off-label use of these pharmaceuticals in other types of tumours but with the same molecular aberration, is a challenging issue.

Depending on the results of the evaluation, the various following steps could be taken:

- a) There is not enough evidence to hand as yet to formulate a reliable conclusion on the safety and/or the efficacy (and, as the case may, the cost-effectiveness) of the therapy but there is enough potential to indicate that the impact of the therapy will be favourable. → Proceed to step 5.
- b) There is insufficient reliable evidence to hand and it is unlikely that this can/will become available in the short term. → Case-by-case evaluation to check whether the use should be supported and which measures could be taken. Elements that could be taken into consideration are the severity of the condition, the alternatives available, the size of the population, the cost of the intervention (both to the authorities and to the patient), budget impact, etc.
- c) If, based on the current knowledge, the off-label use shows little potential for positive results, it would be wiser not to support the use in question. And if there is evidence of contraindications, it would be best to restrict off-label use altogether. This could be effected by advising against the off-label use in a practice guideline issued by a professional organisation of doctors. Another option would be that the competent bodies (FAMHP or EMA) list the off-label use as a contraindication on the leaflet. On occasions, the FAMHP already publishes warnings with regard to off-label use within the framework of pharmacovigilance. → In these cases the step-by-step plan ends unless new evidence and information comes to light to change this stance, with the result that a new evaluation becomes desirable.
- d) Yes, there is enough reliable evidence to hand to support the off-label use. → Proceed to step 6.

j A line extension is a marketing authorisation for the same marketing authorisation holder, where for instance the pharmaceutical form and/or strength differs from one or more other pharmaceutical products for which the applicant already holds a marketing authorisation.

Step 5: Is the manufacturer prepared to generate further evidence?

If the safety and efficacy of the off-label use has not been adequately demonstrated but if the possibility of added value for patients and society is great, the manufacturer could be asked to conduct further research into supporting evidence within a reasonable period of time.

- **If the manufacturer is prepared to engage in further research**, arrangements could be made about study design, the relevant comparator(s) and endpoints, for instance.
- **If the manufacturer declines,** he cannot be forced to conduct a clinical trial on the safety and efficacy of the off-label use of his product (see section 3.1).

  In cases where a study like this would be of sufficient interest to society and the manufacturer has no (financial) interest in conducting a clinical trial himself, the authorities could consider providing the necessary funding (see KCE report 246 Publicly funded Practice-oriented Clinical Trials[20]) once the FAMHP has confirmed that the non-clinical file warrants a clinical trial in the new application. This non-clinical part is a.o. relevant if the new indication is an application for chronic use and applications for one-off use only have been authorised because, in that case, the toxicology would be different. The effect of the medicinal product should then for instance be examined in extended animal tests.

  A clinical trial by the authorities is not recommended if the manufacturer himself has every interest in conducting the study.

Following a positive evaluation of the non-clinical and clinical data by the competent authorities (FAMHP/EMA), the clinical data could also be separately assessed by the NIHDI or KCE with a view to suitable funding.

The next stage in the step-by-step plan will be dictated by the result of the study funded by the manufacturer or the authorities and/or the other research data available. In the event of a negative result, measures could be introduced to curtail the off-label use (see step 4c). In the case of a positive result (step 4d), step 6 can be proceeded to.

Step 6: Is the manufacturer prepared to apply for an MA?

As stated earlier (see section 1.5), pharmaceutical companies do not always stand anything to gain, be it financially or legally, from applying for an extension for the use of a medicinal product that is authorised already, in spite of the European measures designed to encourage this (see section 2.3). Yet, an arrangement at European level where the off-label use goes through the authorisation process and is authorised would be preferable.

In some cases, the manufacturer may not have the relevant rights to develop an off-label indication. As patent holder, the manufacturer is, in principle, the only one entitled to exploit the medicinal product. But he may sell a user right - a licence - to third parties. So, in principle, several manufacturers could have a licence for a different therapeutic indication of one and the same product.

Could the authorities compel manufacturers to apply for an extension of or a variation on the MA if they do own the rights but are unwilling to do so? In principle, that does not seem an option in view of the freedom to conduct a business and the manufacturer's rights in and responsibilities for a medicinal product (see scientific report 7.2.1.). A measure of this nature would be overly drastic and, as a consequence, would be deemed to be disproportionate. After all, there are other, less radical, ways to guarantee responsible use (see step 8).

On the other hand, as was pointed out earlier, it is next to impossible for a third party to apply for an MA in view of the investment that would be required and because they often do not have the relevant data (including the non-clinical file) to hand to build a solid file.

Whether a manufacturer is prepared to apply for an (extension of an) MA for off-label use underpinned by reliable evidence will, as a consequence, also determine the further course of this step-by-step plan:

- **The manufacturer is prepared to file an MA application**. Once the MA is finally granted, off-label use is no longer an issue and the traditional procedure for (the extension of) a reimbursement can be started up.

- **The manufacturer does not want to file an MA application**. → Proceed to step 7.

  If a manufacturer refuses to file an application due to pricing or market arrangements, penalties can be imposed, but that does still not create an obligation to apply for an MA for the off-label use in question.

However, the existing scientific information could be disseminated amongst the medical profession. Aside from generating evidence, Europe could compel the manufacturer to disclose information (e.g. data from pharmacovigilance studies or other research) to the EMA, so that this could be incorporated into the leaflet or into a European Public Assessment Report[k], as far as this was not already done.

Step 7: Is entering into price negotiations with manufacturers of an authorised alternative an option?

If a more expensive authorised alternative is available and the manufacturer of the off-label medicinal product does not want to apply for an MA, the authorities can **enter into price negotiations with the manufacturer of the authorised alternative.** This would allow the authorities, if the relevant evidence is available, to argue that the (cheaper) off-label product is equivalent to the authorised product. The outcome of these negotiations would be decisive for the next steps the authorities could take:

- **The manufacturer is prepared to reduce the price of the authorised medicinal product sufficiently**. If there is little difference in the added value of the interventions, this would lead to a price reduction to the price level of the cheapest alternative. In this case, the authorities could reward the manufacturer of the authorised alternative by no longer financiallly supporting the off-label use of the medicinal product.
- **The manufacturer is unwilling to enter into negotiations** about the price of the authorised product or the negotiations do not produce the desired result. → Proceed to step 8.

- If there are no more expensive **authorised alternatives** than the off-label product, this step is irrelevant and step 8 can be proceeded to.

In all of this it needs to be emphasised that a manufacturer takes decisions within an international, not to say global, price negotiation strategy. At that, local price negotiations between a manufacturer and hospital pharmacies usually tend to relate to several medicinal products at once. Besides, several hospitals can sometimes operate a joint procurement policy. Local and isolated incentives should therefore be interpreted in this context which is why they do not always produce the desired effect.

Step 8: Options as regards financial support for off-label use

- **Art. 56 Agreement**

  Pending a further optimisation of the legislation, the reimbursement of some off-label medicinal products could be regulated via an art. 56 agreement[21] (between NIHDI and a group of doctors). An agreement like this could impose quality requirements as regards processing and/or use.

- **In hospitals: fixed amount per patient suffering from a certain condition**

  If off-label use is scientifically substantiated and cost-effective, the authorities could provide financial support to facilitate the use of the product. For one, a fixed amount could be disbursed (remuneration category F[l]) that is slightly higher than the cheapest (off-label) alternative. In turn, hospitals could then use the extra income generated from the use of the cheaper product to cover the cost of the more expensive authorised product. In fact, only the most expensive product will be an option/justified for some patients, for instance because they are unable to tolerate the other products.

  The decision to opt for a particular medicinal product will always remain the doctor's to take. What matters is that he informs the patient about

[k] On the basis of the assessment report compiled to evaluate the MA application, a European Public Assessment Report (EPAR) can then be prepared and published on the EMA website.

[l] Class F is a reimbursement category for vital specialities (Erythropotins (EPO)) or for therapeutically important pharmaceutical specialities (medicinal products used to treat macular degeneration) that are reimbursed on a fixed amount basis. The difference, if any, between the price and the reimbursement basis cannot be passed on to the patient. http://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/Paginas/unmet-medical-need.aspx

the off-label use and that the latter gives his informed consent. In this way, responsibility is shared between doctor and patient.

- **Out-patient care and day hospital admissions: reimbursement per intervention, including the medicinal products used**

  In the outpatient sector, an intervention-specific reimbursement system could be put in place which covers both the fee and the equipment (medicinal products and others). In private outpatient care, the doctor could then for instance settle the price of the medicinal product with the pharmacist. In this scenario too, the doctor remains responsible for the choice of the most appropriate medicinal product.

  Should the authorities also wish to foster transparency about the use of products, the necessary additional measures, such as a suitable registration system, will have to be introduced.

  Finally, the authorities can also stimulate the extension of indications via their reimbursement policy. As stated earlier, the authorities could, once an extension has been granted, ask the manufacturer for a **global price reduction of the medicinal product**, based on the argument that manufacturers will also generate a greater turnover. In practice however, manufacturers already generate revenue from off-label use as it is without having to bother with additional investment. A price policy that does not penalise the extension of indications plus enhanced transparency as regards off-label use might entice manufacturers to apply for MA extensions.

Is this step-by-step plan in conformity with European legislation?

The supporting of off-label use, where authorised alternatives are available, is characterised by a tension between on the one hand public health interests, where economic aspects, in times of budgetary constraints, play a role and on the other hand a European regulatory system set up to encourage research and development of innovative and safe pharmaceuticals. Therefore, it is difficult to strike a balance between these differing and at the same time complementary interests.

Member States are vested with the powers to set their own healthcare policy priorities provided these do not contravene EU legislation. They have complete autonomy when it comes to deciding where public resources are spent. The above schedule could help them to ensure safe and effective off-label use.

It clearly prioritises the protection of public health over and above any economic, budgetary considerations. This applies to each of the main measures in the step-by-step plan:

- **Publicly funded trials** facilitate access to safe medicinal products and proactively prevent harmful and widespread off-label use.
- **Reimbursement** of off-label use is considered only if there is sufficient clinical and non-clinical scientific evidence to hand during the assessment (comparable to the evaluation of MA applications). Where there is insufficient evidence or if the evidence is stacked against the off-label use, its use is banned or limited to certain, justified cases which, in turn, also ensures optimum protection of public health. MA holders of the authorised product are actually consulted in every step of the way. Financial support from the authorities for evidence-based off-label use is considered only if all other options have been exhausted. In this sense, the proportionality of the measure is also guaranteed.

The final and exclusive decision-making powers to use a medicinal product in an individual case remain with the doctor, after he has obtained the patient's informed consent. The proposed measures do not prevent the patient from making the best possible personal therapeutic choice. They allow patients to choose for an off-label used pharmaceutical based on the available or generated evidence. In this individual choice, cost considerations can also play a role. As mentioned earlier in the examples (e.g. off-label use of Caffeïne Sterop instead of Peyona), in some cases where orphan drugs are not reimbursed, patients will have to bear the costs themselves or can (if needed) opt for a cheaper off-label alternative.

RECOMMENDATIONS[13]

To the FPS Public Health and the prescribing doctors

General provision of information

- **Doctors should be informed of the legal framework within which they can prescribe off-label so that they know that off-label is permitted provided that:**
  - **They carefully consider whether the off-label use is indicated in the given circumstances (on the basis of clinical and non-clinical scientific evidence, the patient's condition, existing alternatives, etc.);**
  - **They have explicitly informed the patient about the off-label use, about the possible alternatives and consequences and the patient has given his or her informed consent.**
- **Doctors should record in the patient file that a medicinal product was prescribed off-label.**

To the Belgian Centre for Pharmacotherapeutic information

- **The Belgian Centre for Pharmacotherapeutic Information (BCFI) could provide a search function on its website to facilitate medicinal products being searched by indication, with specifications as to price and reimbursement. This could be updated with scientific results on off-label use.**

To the FAMHP/EMA, NIHDI and the scientific organisations of physicians concerned

The step-by-step plan for the evaluation of widespread or increased off-label use or off-label use with potential evidence of safety and efficacy should be applied.

Requests to assess medicinal products used off-label

<u>No authorised alternative available</u>

- **In case of off-label use of a pharmaceutical, where no (authorised) alterative, pharmaceutical or not, is available on the Belgian market, it should be examined whether the medical need, compassionate use and unmet medical need programs can be applied and whether the producer is willing to use them. An evaluation of these programs should be scheduled.**

13 The KCE has sole responsibility for the recommendations.

Authorised alternative available

- **In cases of widespread or increased off-label use, each interested party can file an application with the FAGG/EMA (depending on the respective competences) to assess the quality, safety and efficacy of the off-label medicinal product. The evaluation could take place via an extension of the existing procedure scientific-technical advice, if necessary with the support of the expertise of relevant other parties.**

Price negotiations and financing supported by evidence

- **If there is sound evidence of the safety and efficacy of an off-label medicinal product, its manufacturer should be encouraged to apply for an MA and reimbursement for off-label use. If he is not prepared to do so, the authorities could base their reimbursement decision on the clinical added value.**
- **If a more expensive authorised alternative is available, price negotiations could lead to a situation where incentives for off-label use disappear.**
- **Re-evaluate the policy of a global price reduction when an indication is extended so as to encourage manufacturers to apply for an extension of their MA.**

To the relevant instances at the European level

- **It should be possible to impose applicants requesting for an MA for a particular indication to include all public and for him available information on off-label use in the file.**
- **The elaboration of an evaluation procedure and the support of justified off-label use should be scheduled on the agenda of the working group "Safe and Timely Access to Medicines for Patients" (STAMP).**

Research agenda

At the European level, procedures should be developed to make the relevant quality- and non-clinical data of the MA holder available when a clinical study on off-label use is designed.

COLOPHON

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Authors:	Celine Vannieuwenhuysen (EQUAL), Pierre Slegers (EQUAL), Mattias Neyt (KCE), Frank Hulstaert (KCE), Sabine Stordeur (KCE), Irina Cleemput (KCE), Irm Vinck (KCE)
Project coordinator and Senior supervisor:	Sabine Stordeur (KCE)
Reviewers:	Irina Cleemput (KCE), Carine Van de Voorde (KCE)
External experts / Stakeholders:	Francis Arickx (RIZIV – INAMI), Lode De Bot (Vlaams PatientenPlatform), Marc Dooms (UZ Leuven), Els Geeraerts (FAGG – AFMPS), Heidi Goethals (Christelijke Mutualiteit), Denis Lacombe (EORTC), Stéphane Lejeune (EORTC), Greet Musch (AFMPS – FAGG), Leo Neels (CEO pharma.be till 2012), Johan Van Calster (FOD Volksgezondheid – SPF Santé publique; CLIVAN), Martine Van Hecke (Test-Aankoop), An Vijverman (Dewallens & Partners Advocatenkantoor)
External validators:	Steffen Thirstrup (NDA Advisory Services),Hugo Robays (Ugent), Peter Bogaert (Covington & Burling LLP)
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