



Study on off-label use of medicinal products in the European Union





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Abstract

European Union (EU) legislation on marketing authorisation of medicinal products aims to safeguard public health and to protect the free movement of these products. As part of this authorisation, the terms under which a product can be used safely and effectively are described in the product information. However, medicinal products might be prescribed and used outside these terms; this is what is called 'off-label use'. This report describes a study on the complex field of off-label use. It covers the public health aspects related to the off-label use of medicinal products. In particular, it investigates the balance between the benefits and risks that off-label use has for patients, and the regulatory framework for the off-label use of medicines.

Applying a wide range of methods, including a systematic review of scientific literature and grey literature, a legal analysis, interviews with stakeholders and an expert meeting, this study provides information on a variety of aspects of off-label use. These include the prevalence and incidence of off-label use and its drivers as well as a description of the national frameworks, regulatory and other, governing off-label use of medicinal products in the various EU Member States. A factual analysis is provided of how authorities have addressed the issue of off-label use and the different ways patients, healthcare professionals and industry react to this. The report does not provide any recommendations.



Executive summary

Off-label use

Legislation on medicinal products in the European Union (EU) regulates the market access of these products by setting standards of safety, quality and efficacy. With this legislation, the EU aims to safeguard public health and to protect the free movement of medicinal products. The terms under which a medicinal product can be used safely and efficaciously are established during the marketing authorisation procedure. These are described in the product information, which is an integral part of the marketing authorisation process. The product information includes the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet. The terms as expressed in the product information are the basis of information for healthcare professionals on how to use the medicinal product. In daily practice, however, medicinal products are not always used in accordance with these terms described; they may be used off-label.

Off-label use refers to any intentional use of an authorised product not covered by the terms of its marketing authorisation and therefore not in accordance with the SmPC. This may for example be the use for a different indication, use of a different dosage, dosing frequency or duration of use, use of a different method of administration, or use by a different patient group (e.g. children instead of adults).

Objectives

This study covers the public health aspects related to the off-label use of medicinal products. In particular, it investigates the balance between the benefits and risks for patients, and the regulatory framework for the off-label use of medicines.

The *general objective* of this report is to provide a description of existing and planned practices regarding off-label use across Member States. This description is complemented by a factual analysis of the positions of all parties towards the existing measures and towards the possible future tools to regulate off-label use at a national level. The study focuses on off-label use of medicinal products for human use and does not cover medicinal products for veterinary use and medical devices. Unauthorised medicinal products are also beyond the scope of this report.

The *specific objectives* of the study are:

1. Providing information on the prevalence and incidence of off-label use, and on its drivers;
2. Providing information on the national frameworks, regulatory and other, governing the off-label use of medicinal products in various EU Member States. This includes describing how authorities have addressed the issue and the different ways patients, healthcare professionals and industry have reacted to this;
3. Providing a factual analysis taking into account the EU legal framework for off-label use and practices in the EU Member States. This includes national legislation and case law. The study identifies particular aspects and/or therapeutic areas of off-label use that merit specific attention at the EU level.

This study only provides a factual analysis and does not give any recommendations.



Methodology

- As a starting point, the legal framework was described. A distinction was made between the regulation of medicinal products and the use of medicinal products in daily practice. The purpose of this description was to provide the context of off-label use. This description was supplemented with a legal analysis on the basis of case law relevant to off-label use (and related issues) from the Court of Justice of the European Union, as well as from national courts of the EU Member States.
- A systematic literature study of the scientific literature was performed with the purpose of collecting information on the extent of off-label use in all EU Member States, the factors driving off-label use, and particular areas of interest. The analysis of the scientific literature study was supplemented with a review of grey literature.
- Stakeholders were consulted by interviews and an expert meeting was held in order to provide an overview of the positions of parties on existing and any new measures/tools. These stakeholders also gave their views on the pros and cons of these measures/tools. The following stakeholder groups were included: (1) representatives of regulatory authorities, (2) representatives of health technology assessment/ pricing and reimbursement bodies, (3) patients, (4) healthcare professionals, (5) pharmaceutical industry, and (6) experts on off-label use.

The legal framework

It is important to distinguish the regulation of medicinal products from their use in medical practice.

Regulation of medicinal products

The EU established legislation to harmonise national legislation in order to safeguard public health and to achieve the goal of a single market for medicinal products. The requirement of a marketing authorisation is a general rule in the legal framework of medicinal products. According to article 6(1) of Directive 2001/83/EC, it is in principle prohibited to market medicinal products without a marketing authorisation. The decision to grant or refuse a marketing authorisation is based on an assessment of the quality, efficacy and safety of the medicinal product and a benefit/risk assessment performed by EMA via its Scientific Committees and by the national competent authorities.

Use of medicinal products in medical practice

EU legislation does not regulate the way medicinal products are ultimately used in medical practice. The prescribing of a medicinal product, on-label or off-label, is a decision taken within the relationship between a patient and his or her treating healthcare professional (HCP). The way Member States organise their healthcare system and the way HCPs conduct their practice is not a topic that falls within the remit of the EU. The EU has limited competence in the field of public health; the ultimate responsibility for the definition of health policy and the delivery of health services and medical care lies with the Member States (Article 168 (7) TFEU). The European Court of Justice indeed confirmed that "*off-label prescribing is not prohibited, or even regulated, by EU law*" and that "*There is no provision which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted.*" (T-452/14 Laboratoires CTRS v Commission, paragraph 79). Off-label use is however recognised as a concept by EU pharmaceutical law (recital 2 of Paediatric Regulation and pharmacovigilance provisions in Directive 2010/84/EU).



Other relevant legislation

Off-label use is also subject to the following other pieces of legislation:

- Liability legislation governs off-label prescribing, dealing with both EU product liability and professional liability. Frequently, off-label prescribing will be in line with the standard of care of HCPs, but off-label as well as on-label prescriptions can be inappropriate, and this may lead to liability.
- HCPs have to comply with ethical and professional standards monitored by disciplinary boards and committees.
- Criminal law also applies to the work of HCPs.
- Reimbursement of off-label use depends on the national health insurance legislation.

Incentives to stimulate innovation

It is within the competences of the EU to establish incentives for the research and development of innovative products and to encourage the marketing authorisation of medicinal products which fulfil a medical need. In the recent past, the EU has adopted the Paediatric Regulation (Regulation 1901/2006/EC) and the Orphan Medicinal Product (Regulation 141/2000/EC). In theory, both regulations could have a decreasing effect on off-label use, because more on-label options may become available. However, at the moment their exact effect on off-label use is unknown.

Case law

In various cases, the European Court of Justice reflected on the marketing authorisation system as established in the EU legislation and the powers of the of the European Commission in regulating medicinal products. An important court case is *European Commission v Republic of Poland* where the court clarified the meaning of article 5 (1) of Directive 2001/83 and emphasised that the exemption to the marketing authorisation requirement cannot be applied for only financial considerations. National courts cases about off-label use relate to a large extent to reimbursement. These cases indicate that additional requirements may apply, including the limitation to life-threatening or severe conditions and the absence of alternative treatment options. Other national court cases concern the (professional) liability prescribing or dispensing medicinal products off-label.

Main findings

The extent of off-label use

Data from scientific literature reveal that the prevalence of off-label use in the EU within the paediatric population is generally high, covers a broad range of therapeutic areas and is common practice for many prescribers in both the hospital and the outpatient settings. Thirty-two studies which took place in various paediatric populations within a hospital setting (covering data from 16 EU Member States) showed that a range of 13-69% of the prescriptions investigated was off-label. In forty studies in the outpatient setting (covering data from 12 Member States) there was a range of 2-100%. A similar pattern was observed for the adult population. Twenty-three studies in various adult populations in an inpatient setting (covering data from six Member States) showed that a range of 7-95% of the prescriptions investigated being off-label. In 13 studies in the outpatient setting (covering data from six Member States) a range of 6-72% was found. Variation in off-label prevalence is not only observed between but also within countries, depending for example on the methodology used and the population studied. A comparison of prevalence figures between the various EU Member States is therefore not possible, but it is apparent that the majority of, if not all, EU Member States are faced with off-label use of medicinal products to some extent.



Areas of interest

Literature data reveals that pharmacotherapy in children and orphan diseases remain areas of particular interest, since off-label use within these areas is still widespread. This was also confirmed by all stakeholder groups in the interviews. Elderly patients (according to regulatory representatives, HCPs and independent experts) and pregnant women (according to all stakeholder groups) may also deserve special attention; although less information on the extent of off-label use in these two groups is available. According to literature, clinical areas of interest regarding off-label use are oncology/haematology, psychiatry and rheumatology. These all represent unmet medical needs. These clinical areas were also mentioned by all stakeholder groups.

Marketing authorisation process

There are limited incentives for pharmaceutical industry to extend the labelling of existing medicinal products; legislation allows for a one year extra market protection if a new indication is registered in the first eight years after a marketing authorisation has been granted and if this new indication brings significant clinical benefit over existing therapies; however, off-label sales will continue without investment in such a new indication anyway; and specifically for off-patent products, generic competition and/or low medicinal product price have a negative impact on return for investments in new indications (source: literature; interviewees patient organisations: EAASM; interviewees professional organisations: UEMS; interviewees industry: EFPIA)

The driving factors regarding off-label use

Various drivers may provoke off-label use of medicinal products. These drivers relate to the marketing authorisation process, post marketing authorisation events (e.g. withdrawal from the market/product not available), pricing and reimbursement, aspects connected with the work of HCPs, and patient related factors. According to literature and stakeholders (patients, HCPs, pharmaceutical industry), there are limited incentives for the pharmaceutical industry to extend the labelling of existing medicinal products, especially for off-patent products. Literature and stakeholders (regulatory, reimbursement, patients) also mention the increase in requirements for marketing authorisation over the years as well as the sometimes long development times and high costs to investigate a new indication. And in some Member States products are not available due to economic reasons (according to all stakeholder groups). Another factor frequently mentioned (by regulatory representatives, patients, HCPs and pharmaceutical industry) was pricing and reimbursement. An important driver on a patient and HCP level is the fact that there is sometimes no other choice than prescribing off-label (mentioned in literature and all stakeholder groups). Also pressure from patients insisting on pharmacotherapy was indicated as driver in literature and by many stakeholders (except by reimbursement and industry stakeholders). In specific cases, it is not a single driver, but rather a combination of drivers that provoke off-label use. Drivers may also change during the life cycle of a medicinal product that is used off-label. Overall, the nature of the drivers is sometimes complex and drivers may interact with each other, however the relative contribution of, and interaction between, the different factors is unknown.

Opinions of stakeholders on off-label use

Off-label use has advantages as well as disadvantages. During the interviews, the following pros and cons of off-label use were mentioned by stakeholders:

- According to all types of stakeholders, a major advantage of off-label use is the better access of patients to (innovative) treatments and the fulfilment of medical needs of patients, especially in cases where no other options are available;



- Another positive element, mainly mentioned by regulators and policy makers in the field of reimbursement, is the potential economic advantage: off-label use contributes to sustainability of the healthcare system. However, stakeholders also see disadvantages when economic reasons are prevailing, such as friction between national authorities and the pharmaceutical industry.
- The issue of liability in case of negative consequences of off-label use is a concern for many stakeholders from different backgrounds.

National frameworks in EU Member States

This study shows that the way Member States are dealing with off-label use is not harmonised. Ten out of the 21 countries that participated in the study have specific policy tools in place for off-label use.

Examples of policy tools incorporated by EU Member States are:

- Legal frameworks to issue temporary recommendations for use and permission to prescribe off-label such as the “temporary recommendations for use (RTU) scheme” in France and the Hungarian system where prescribers or their organisations have to ask for permission to prescribe a product off-label.
- Measures to regulate reimbursement, for example France and Italy explicitly allow for reimbursement of off-label use also when (on-label/authorized/not strictly identical) alternatives exist.
- Policy tools providing guidance for prescribers such as the General Medical Council Guidance (Good practice in prescribing and managing medicines and devices, 2013) in the UK.
- Policy tools where professional standards are leading, such as The Netherlands where off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use.
- Policy tools focused on the patient, for example regarding the necessity to give informed consent needed in many Member States or the fact that for serious interventions, upon request of the patient, a HCP has to register for what intervention the patient has given consent (The Netherlands).

In EU Member States without specific policy tools on off-label use, the dominant view is that off-label use is an issue to be dealt with at the level of the prescriber rather than at the regulatory or healthcare system level. Prescribers are trusted to know what is best for the well-being of the patient, with the medical need of the patient leading their decisions. Yet, it is also mentioned that lack of clarity about the liability is an issue in case of off-label prescribing and that patients should be properly informed and provide consent.

A set of policy options was explored based upon the information about the legal frameworks, the driving factors and the practices in Member States (see below). The general conclusion is that a variety of policy options at different levels is possible in the complex field of off-label use. Generally, the so-called ‘soft approaches’, such as providing guidelines and collecting evidence in practice on off-label use, have the widest support among all stakeholders.

Policy options on a regulatory level

Stakeholders in an expert meeting were consulted on their opinion on a variety of potential measures, nationally or at the EU-level, that could be taken in the field of



off-label use. Below a summary of the opinions stated in the expert meeting is provided. If a certain group of stakeholders had an opinion that clearly differed from the group, this is explicitly mentioned.

According to the stakeholders in the expert meeting, the EU could act on off-label use by:

- Exploring the possibilities of including other evidence than industry-based Randomised Controlled Trials (RCTs) for the marketing authorisation of off-label indications and other modalities, and the conditions under which this would be possible. Evidence from monitoring patient cohorts, data from routine patient registries and from reporting adverse events, voluntarily or otherwise, are examples of other sources of data. This option is especially useful for those situations where RCTs are hard to organise, for example due to a low number of eligible patients.
- Providing guidance for Member States on off-label use, for example by developing general advice on off-label use that provides direction for the development of national guidelines. An example of this would be on the elements to be included in treatment guidelines in case of off-label use. This would also provide common ground for the development of national treatment guidelines in the individual EU Member States.
- Creating/enhancing incentives for pharmaceutical companies to register new indications and other modalities (such as dosing, formulation) for existing products, taking into account the revenues of the Paediatric Regulation, the Orphan Medicinal Product Regulation and the one-year extra market protection option in cases where there are new indications for products already authorised (included in Directive 2001/83/EC).

Policy options on a healthcare system level

According to the stakeholders in the expert meeting, the Member States could act on off-label use by:

- Asking prescribers to apply for permission to prescribe off-label with the competent authority. This authority could then evaluate the evidence on efficacy and safety, thus offering a balance between the benefits and risks of off-label use for patients.
- Reimbursement measures can also have an influence on off-label use, for example where the off-label product is not reimbursed. Sometimes an off-label product is reimbursed while its on-label competitor is not, which has resulted in much debate.

Policy options on the HCP-patient level

The stakeholders in the expert meeting, there are also options focussing more directly on HCPs and their patients. These include:

- The development of treatment guidelines by professional bodies at the national level.
- Improved patient information, preferably in the form of individual messages to patients provided by HCPs accompanied by easily accessible online and printed information.



1. Introduction

1.1 Background

The EU legal framework for medicinal products for human use regulates the authorisation of medicinal products by setting standards of safety, quality and efficacy. The main objective of the EU pharmaceutical legislation is to safeguard public health while protecting free movement of medicinal products. The main objectives of the EU legislation on medicinal products are to protect public health in application of Article 168 of the Treaty on the functioning of the European Union (TFEU) and to ensure the free movement of medicinal products in the EU in accordance with Article 114 of TFEU. An authorisation is required for all medicinal products before entering the EU market. During the marketing authorisation procedure, the conditions are established under which the product can be used safely and efficaciously. The Summary of Product Characteristics (SmPC) describes these terms and is the basis of information for healthcare professionals on how to use the medicinal product. However, sometimes products are used off-label. Off-label use can be defined as *any intentional use of an authorised product not covered by the terms of its marketing authorisation and therewith not in accordance with the Summary of Product Characteristics (SmPC)*.^{a,b} Off-label use may refer to the use for a different indication, use of a different dosage, dosing frequency or duration of use, use of a different method of administration, or use by a different patient group (e.g. children instead of adults). Whereas market approval of medicinal products is the subject to EU legislation and falls under the responsibility of the national competent authorities or, in case of a centralised procedure, the European Commission (EC), EU legislation does not regulate the use of medicinal products in medical practice.

Scope of this report

This report provides a description of existing and foreseen practices of off-label use across EU Member States. This description is supplemented with a factual analysis of all parties' positions towards the existing measures and possible future tools to regulate off-label use at EU or national level. The study focuses on off-label use of medicinal products for human use and does not cover medicinal products for veterinary use and medical devices.

Unauthorised medicinal products are also out of the scope of this report. Unauthorised medicinal products do not have a marketing authorisation in the EU member state where they are being used.^{1,c} With a few exceptions, the use of unauthorised products is forbidden; the exceptions include:

- The use of an unauthorised product in a clinical trial regulated by Directive 2001/20/EC on the conduct of clinical trials, as set out in Article 3 of Directive 2001/83/EC;
- In case of magistral and officinal products prepared in a pharmacy, as set out in Article 3 of Directive 2001/83/EC;

^a In some EU Member States the term 'off-label' includes compassionate use. If this is the case (for example because we report about a study using a broader definition than above-mentioned), this will be explicitly mentioned and the definition used will be clearly described.

^b It is noted that SmPCs might, for historical reasons, sometimes differ per Member State. As such it may well be that off-label use in Member State A is not off-label in Member State B.

^c Numbers in superscript refer to the reference list at the end of the report.



- Other exceptions in Directive 2001/83/EC (article 5) and Regulation 726/2004/EC:
 - Special needs: article 5 (1) of Directive 2001-/83/EC states: “A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility”;
 - Emergency situations: article 5(2) of Directive 2001-/83/EC states: “Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm”;
 - Compassionate use (Regulation 726/2004/EC, article 83) refers to making an unauthorised medicinal “available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trial”.

1.1.1 Marketing authorisation and post-market surveillance

Authorisation

As stated above, all medicinal products require a marketing authorisation before entering the market. The EC, the EMA and the EU Member State competent authorities are working closely together to assure that all medicinal products for humans introduced to the European market meet the EU standards on quality, safety and efficacy. During the authorisation process, a competent authority evaluates the quality, efficacy and safety of the product, including its benefit-risk balance.

Marketing authorisation can be obtained by different routes (see also chapter 3.1.2).^d Irrespective of the authorisation route, a favourable balance between beneficial and harmful effects of a medicinal product in the proposed therapeutic indication and the proposed patient population must be demonstrated. The basis for this is a dossier submitted to the authorities by the applicant. The dossier includes quality, preclinical and clinical evidence for the proposed indication, patient population and other modalities, such as dosage frequency and method of administration. An indication or a modality of use that is not claimed by the applicant will not appear in the official product information, unless it is listed as a contraindication or warning.

Product information

During the marketing authorisation procedure, for each medicinal product the official product information is approved: the Summary of Product Characteristics (SmPC)^e. The Package Leaflet is derived from this SmPC. The official product information is authorised by competent authorities of the Member States (in accordance with Directive 2001/83/EC) or, in case of a centralised procedure, by the EC (in accordance with Regulation (EC) No 726/2004). The SmPC includes the definitive description of the product, both in terms of its properties (e.g. chemical, pharmacological) and how the product is to be used for a specific treatment. It sets out the position of the

^d http://www.ema.europa.eu/docs/en_GB/document_library/Brochure/2014/08/WC500171674.pdf (August 10, 2016)

^e http://ec.europa.eu/health/files/eudralex/vol-2/c/smcp_guideline_rev2_en.pdf (January 25, 2017)



medicinal product as distilled during the course of the assessment process and agreed between the applicant and the competent authority. Once the product is approved, the SmPC cannot be changed, except when the competent authority approves such a change. In daily practice, medicinal products are not always used in accordance with the SmPC; they may be used at the discretion of the HCP.

Monitoring during lifespan of a medicinal product

The medicinal product may be used by other groups of patients than included in the pre-market stage (randomised) clinical trials (RCTs). Moreover, the products may be used for a longer time period and in a larger population than included in the RCTs. This may lead to the discovery of side effects that did not become known in the pre-marketing stage. In order to monitor safety of authorised products placed on the market during their entire lifespan, the EU has set pharmacovigilance rules and related measures. In accordance with these rules, the safety of medicines is monitored and actions to reduce the risks and increase the benefits of medicines are taken.^f In July 2012, new pharmacovigilance legislation became effective. Its major aim is to reduce the number of adverse drug reactions (ADRs) in the EU through:

- “the collection of better data on medicines and their safety;
- rapid and robust assessment of issues related to the safety of medicines;
- effective regulatory action to deliver safe and efficacious use of medicines;
- empowerment of patients through reporting and participation;
- increased levels of transparency and better communication”.^g

These measures are taken in order to ensure that in case of adverse reactions appropriate actions can be taken, such as additional warnings, restrictions of use or even suspension or revocation of the marketing authorisation. With the new pharmacovigilance legislation, the definition of ADR was extended to include off-label use.

1.1.2 Off-label use

Off-label prescribing is part of medical practice and may be necessary to fulfil the need of individual patients, due to the absence of suitable, authorized alternatives. Off-label use can be fully rational and sometimes is the only treatment option for the patient. As such, off-label use cannot be fully avoided, since there will always be individual situations where the available, authorized products’ arsenal does not meet the patient’s need. Although EU-legislation does not directly regulate off-label use, off-label use received particular attention in the new EU pharmacovigilance legislation. Directive 2010/84/EU acknowledges that off-label use exists and states that marketing authorisation holders (MAHs) are responsible to provide all available information on their products – including the results of clinical trials or other studies – as well as any use of the product outside the terms of its marketing authorisation.

In order to decrease the barriers to apply for market authorisation of a new indication of an existing product and to fulfil a medical need, four measures have been taken at EU-level. These include the one-year extra market protection option in case of new indications for already authorised products (included in Directive 2001/83/EC), the one-year data exclusivity for new therapeutic indication for medicinal products not covered by data exclusivity (included in Directive 2001/83/EC), the introduction of the

^f <http://www.parlementairemonitor.nl/9353000/1/j9vvij5epmj1ey0/vjr0gqnjelwf?ctx=vg9pl2emdcyl&tab=1> (august 10, 2016)

^g http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp



Paediatric Regulation 1901/2006/EC and the introduction of the Orphan Medicinal Product Regulation 141/2000/EC. For this last regulation, a study by Brabers et al. (2011) showed that between April 2000 and 31 December 2008, 58 products obtained marketing approval for the treatment of 44 rare diseases².

The level of evidence to prescribe and use a product off-label use may differ¹. Sometimes, evidence of efficacy and safety is available, but the pharmaceutical company does not take steps to extend the market authorisation. This is for example the case with various medicines used in children: information on efficacy and safety is gathered in clinical practice and made available to HCPs (for example, the Dutch and the British formularies for children), but this evidence does not (always) lead to a formal application to enlarge the age range for the (off-label used) medicinal product. Also bevacizumab (Avastin®) is exemplary. Bevacizumab was registered for intravenous use in different types of cancer. However, soon it was also widely used off-label in the treatment of wet age-related macular degeneration (AMD) (see also section 3.5).³ No steps were taken to extend the marketing authorisation of Bevacizumab with AMD as new indication.

Sometimes high-level evidence is difficult to reach, even for those treatments that might be effective. This situation may arise for rare diseases or in paediatrics when a range of age-appropriate formulations should be developed to serve the various age groups. In those cases, large clinical studies are not easy to perform. For example, Ivanovska et al. performed a review on challenges in children's medicinal products and state that new paediatric formulations address only a small part of the therapeutic needs⁴.

1.2 Objectives

Off-label use of medicinal products has led to an increasing number of questions by Member States and stakeholders towards the European Commission. The Commission services discussed the issue with Member States in the framework of the EU Pharmaceutical Committee. In parallel, the European Parliament adopted a resolution on the implementation of the Council Recommendation (2009/C 151/01) on patient safety, with the two main following requests (October 22, 2013):

- *"Calls on the European Medicines Agency (EMA) to draw up a list of off-label medicinal products which are used in spite of there being an approved alternative" (paragraph 13);*
- *"Calls on the European Medicines Agency to develop guidelines on the off-label use of medicinal products, on the basis of medical need and taking account of patient protection" (paragraph 53).*

The Commission replied to the European Parliament that^h "the issue of off-label use of medicinal products is complex and deserves consideration. EMA could be an important player in that context; however, possible actions of EMA should be seen in an overall context and within the remit of its competences. Calling on EMA to draft a list of medicines used off-label in spite of approved alternative may not be representative, as not all Member States have the same medicinal products on their market (national marketing authorisation through decentralised procedures). In addition, in some Member States recommendations and guidelines have been developed regarding off-label use. Although EU legislation regulates marketing authorisations of medicinal products, it does not specifically regulate the off-label use of products, and the Commission plans to commission a study in 2014 in order to understand the

^h [http://www.europarl.europa.eu/oeil/popups/ficheprocedure.do?reference=2013/2022\(INI\)&l=en#tab-0](http://www.europarl.europa.eu/oeil/popups/ficheprocedure.do?reference=2013/2022(INI)&l=en#tab-0)



ramification of the issue of off-label use of medicinal products. In view of this, the call for action by the European Medicines Agency would be premature.”

This report describes the results of the study. The study covers the public health aspects related to the off-label use of medicinal products, and in particular the balance between its benefits and risks for patients, and the regulatory framework for the off-label use of medicines. The general objective of the study is to provide a description of existing and foreseen practices of off-label use across Member States and a factual analysis of all parties’ positions towards the existing measures and possible envisaged tools to regulate the off-label medicine use at national level.

The **specific objectives** are:

1. Providing information on the prevalence and incidence of off-label use, and on its drivers;
2. Providing information on the national frameworks (regulatory and other) governing off-label use of medicinal products in the various EU Member States; describing how authorities have addressed the issue and the different ways stakeholders (patients, healthcare professionals and industry) react on this;
3. Providing a factual analysis of off-label use and practices in the EU Member States (including national legislation and case law where relevant) against the EU legal framework; identifying particular aspects and/or therapeutic areas of off-label use that would deserve specific attention at EU level.

This study only provides a factual analysis and does not give any recommendations.

1.3 Structure of the report

This remainder of this report contains five chapters:

Chapter 2 (Methods) describes the diversity of methods used in this study to collect information on off-label use in the EU which included:

- A legal analysis based upon a variety of sources including searches in PubMed, Google Scholar and Google; searches in EU and Dutch case law databases; information requests to legal experts with extensive knowledge and experience on pharmaceutical law and consultation of EMACOLEX.
- A systematic literature review (period: 2000-2015) with the purpose of collecting information on the extent and practices of off-label use in all EU Member States and on drivers for off-label use;
- Grey literature review: soliciting stakeholders, subcontractors in the EU Member States and interviewees were asked for relevant publications and grey literature on off-label use in their respective countries
- Stakeholder interviews with the aim to compare the positions of Member State authorities and stakeholders (patients, healthcare professionals, pharmaceutical industry) regarding the existing and any newly identified measures/tools to handle off-label use.
- An expert meeting with as its aim to compare positions of Member State representatives and EU-level stakeholders with a clear synthesis of pros and cons.

Chapter 3 (Legal framework) describes the legislative frameworks of off-label use. It starts with a description of legislation at the EU level which includes a description of the legislation of the regulation of medicinal products where the EU is competent to establish legislation in order to harmonise national legislation in order to safeguard public health and to achieve the goal of a single market for medicinal products. It also includes a description of the use of medicinal products in medical practice. Two



measures that have been taken in order to encourage research and development of innovative products and to encourage marketing authorisation of medicinal products fulfilling a medical need are also shortly discussed: the Paediatric Regulation and Orphan Medicinal Product Regulation. Chapter 3 also describes aspects of national legislative frameworks that are important in relation to off-label use as well as case law on off-label use both at the EU and the individual Member State level.

Chapter 4 (Extent of off-label use and current practices) presents information gathered on different aspects of off-label use. In order to provide a picture of the scope of the problem of off-label use, this chapter starts with an overview of the literature on the extent of off-label use in children and adults in EU Member States and a description of therapeutic areas, specific patient groups and specific situations for therapeutic use that are more prone to off-label use of medicinal products. After exploring the extent of and important areas for off-label use are known, we describe what drives this off-label use. We thereby focus on drivers at different levels: the patient and HCP level, the health care system level and the regulatory level. Off-label use takes place within the health care systems and regulatory settings of the EU Member States. EU Member States can take actions that can have an impact, among other factors, on the extent and nature of off-label use. Chapter 4 therefore also describes which practices are in place with regard to off-label use in EU Member States and whether or not there are new measures in preparation. There are several stakeholders involved in off-label use and their opinions may have an impact on the acceptance of measures for off-label use. Therefore, we assessed both the opinions of stakeholders on off-label use in general as well as on the pros and cons of different measures in the field of off-label use.

Chapter 5 (Analysis)

This chapter starts with an analysis of the EU legal framework and the interplay with national regulations, followed by an analysis of the impact of two EU-level measures on off-label use: EU Paediatric Regulation and EU Regulation on Orphan Medicinal products on the off-label use of medicinal products. Next, a variety of policy options in the field of off-label use (derived from chapter 4) are analysed. For each of the policy options the following aspects are considered: the content of the policy option, the impact of the policy option on patients, health care professionals, and the health care and regulatory system; consequences in terms of liability; the position of different stakeholders on this option and the interplay with and implications regarding the EU regulatory framework. These policy options are also related to the drivers of off-label use to see whether and how policy options can influence the forces that drive off-label use. Finally, all information available and relevant to areas of specific interest for off-label (such as children, the elderly and pregnant women) are described.

Chapter 6 (Summary of results and conclusion) summarises all key findings.



2. Methods

2.1 Introduction

This chapter describes the methods used in this study. Section 2.2 describes the methods that were used for the legal analysis that aimed to describe the legal framework for off-label use in the EU as well as case law on off-label use. This legal analysis was performed by two lawyers specialised in pharmaceutical law. In section 2.3 the collection and way the literature was analysed, is described. The aim was to collect information on the extent of off-label use in all EU Member States and on drivers for off-label use. Section 2.4 describes the way stakeholders were involved in the study. The aim of the stakeholder consultation was to compare the positions of Member State authorities and stakeholders (patients, healthcare professionals, pharmaceutical industry) regarding the existing and any newly identified measures/tools to handle off-label use, with a synthesis of pros and cons. First, interviews were held, followed by an expert meeting. At the end of each section, it is indicated in which part of the report the respective methods are applied.

2.2 Legal analysis

The aim was to provide the European Commission with an analysis of the EU legal framework. This included case law relevant to on off-label use (and related issues) from the Court of Justice of the European Union, as well as from national courts of the EU Member States. Please note that no normative interpretation to the data and no recommendations were made.

2.2.1 Identification of court cases

The case law was identified through multiple methods including:

- searches in PubMed, Google Scholar and Google;
- searches in EU and Dutch case law databases;
- information requests to legal experts with extensive knowledge and experience on pharmaceutical law;
- the expert meeting with representatives of EU Member states (see section 2.4.2 for detailed information);
- the questionnaire among interviewees EU Member States and EU-level stakeholders (i.e. patients' organisations, healthcare professionals' organisations and pharmaceutical industry) who were asked to provide examples of cases (see section 2.4.1 for detailed information);
- requests to the national contacts of the project team in Member States;
- information from DG Santé;
- consultation of the European Medicines Agencies Co-operation of Legal and Legislative Issues (EMACOLEX).

2.2.2 Analysis of collected information

For the identified court cases, a summary was made, including the issue at stake, the factual background, the arguments of the parties, and the factual outcome of the case. In the factual analysis of the case, facts are presented as far as considered relevant to the legal considerations by the respective court. In case of an appeal procedure the factual analysis primarily focused on the appeal case, while the courts' decision in first instance was only assessed as far as relevant to the appeal.



Considerations and arguments of procedural nature, e.g. the admissibility of a case, were also only assessed as far as relevant to a court's decision.

Where to find the results?

The results of the legal analysis are described in chapter 3 and are also used in chapter 5 which provides an analysis of the EU legal framework and national legislations and practice in EU Member States.

2.3 Literature review

2.3.1 Systematic literature search

A systematic literature study was performed with the purpose of collecting information on the extent of off-label use in all EU Member States and on drivers for off-label use. The electronic databases PubMed and Embase were searched for the period 2000-2015. Search strings were developed and optimized in co-operation with an information specialist. The search was limited to the official languages of the EU Member States.

Publications were included if they met all of the following criteria:

- off-label use of medicinal products for human use is the main subject;
- the extent and kind of off-label use and/or practice and/or drivers regarding off-label use are described;
- the study addresses off-label use/practice within the geographical context of at least one EU Member State;
- the publication is a professionally or scholarly 'sound' publication, i.e. a scientifically peer reviewed publication or a publication from a governmental or professional association.

Publications were excluded if one or more of the following criteria applied:

- the study only relates to unauthorised medicinal products;
- the study only addresses the issue of lack of harmonisation of SmPCs;
- the publication summarises efficacy and/or safety data of a product included in a compassionate use programme.

The search resulted in 872 references. A two-stage inclusion process was applied. First, all references were studied independently by title and abstract by pairs of reviewers and included in the study according to the above-mentioned criteria. Disagreements were resolved by discussion. After this selection process 202 references remained. In the second stage, pairs of researchers independently read the full text of each publication in order to determine whether it fulfilled the inclusion criteria. This resulted in the final inclusion of 125 papers. A distinction was made between prevalence figures reported for children (≤ 18 years) and for adults (> 18 years), and between figures obtained from data gathered inside and outside hospitals.

In order to illustrate several drivers for off-label use, information was gathered on specific cases mentioned by stakeholders in the interviews. This information was found by searching literature in the above-mentioned databases and by searching the internet for grey literature.



2.3.2 Collection of other relevant publications

The electronic databases resulted in some publications that did not fulfil the inclusion criteria, but were considered as relevant (so called 'grey literature', such as meeting reports). We also asked soliciting stakeholders and subcontractors in the EU Member States (through the EPHA-network and through the 23 EPHORT subcontractorsⁱ) for relevant publications and grey literature on off-label use in their respective countries as well as through the respondents of the interviews. This resulted in additional publications on off-label use from Belgium, the Czech Republic, Denmark, France, Hungary, Ireland, the Netherlands, Portugal and Malta as well as some European level documents.

Where to find the results?

The results of the analysis on the extent of off-label use are described in section 4.2 whereas the results on the drivers of off-label use are described in section 4.4. The results of the literature on the practices of off-label use are used for the description of the national frameworks on off-label in section 4.5. The results are also used in the analysis of the policy options in chapter 5.

2.4 Consultation of stakeholders

The literature review was complemented with a stakeholder consultation. The following groups were distinguished: (1) representatives of medicinal product regulatory authorities, (2) representatives of health technology assessment/ pricing and reimbursement bodies, (3) patients, (4) healthcare professionals, (5) pharmaceutical industry, and (6) experts on off-label use. This consultation was held in two steps:

1. Telephone interviews with relevant Member State authorities (regulatory authorities responsible for the licensing of human medicinal products, health technology assessment/pricing and reimbursement bodies or experts in the field of off-label use) and stakeholders (patients, healthcare professionals and pharmaceutical industry) to make an overview of positions of these parties on existing and any new measures/tools, with a synthesis of pros and cons.
2. Brainstorming session/expert meeting with all stakeholders:
 - Member State authorities;
 - Patients & healthcare professionals;
 - Pharmaceutical industry.

So, a qualitative research methodology was applied, not allowing any quantitative analysis and statements (e.g. how many stakeholders were or were not in favour of specific policy tools).

2.4.1 Interviews

The aim of the interviews was to compare the positions of Member State authorities and stakeholders (patients, healthcare professionals, pharmaceutical industry) regarding the existing and any newly identified measures/tools to handle off-label use, with a synthesis of pros and cons.

ⁱ The EPHORT consortium exists of NIVEL, RIVM and EPHA. The consortium has a contact in 23 Member States who can be consulted for questions with regard to research projects of the Consortium in different fields of health care.



Questionnaire

A questionnaire was developed containing seven sections:

1. Background information
2. Off-label use: existing measures and policy tools
3. Extent and practices of off-label use
4. Drivers of off-label use
5. Off-label use: pros and cons
6. Policy tools and/or measures - what is needed
7. Court cases

The full questionnaire can be found in Annex A.

Recruiting representatives from Member States and stakeholders

Interviewees were recruited at national and EU level:

- National authorities: representatives were recruited through a list delivered by DG Santé. This group consisted of: (1) Representatives for authorising and controlling the use of medicinal products, and (2) those responsible for pricing and reimbursement. In every Member State one to three persons from DG Santé list were approached. Once it proved that not all approached persons responded after two reminders, we also asked our contact persons in the Member States for suggestions. Some persons we approached referred us to other persons, mainly the national experts in the field of off-label use; as such they were not representatives of national authorities.
- Stakeholders at EU-level: they were approached through different channels. First, some representatives approached researchers to ask their interest in participation. Second, EPHA approached their network and asked for participation. Third, we searched for relevant stakeholder organisations on the internet.

Data collection

Most representatives were interviewed, but some preferred to fill out the questionnaire on paper, for example in order to be able to consult other stakeholders in their country. Table B.1 in Annex B shows the countries (n=21) which were represented in the interviews. The representatives mainly were regulators or experts in the field of off-label use. Moreover, EU-level stakeholder organisations participated in the interviews (patients: n=4; healthcare professionals: n=5 interviews representing 4 organisations; industry: n=3; regulatory body (EMA): n=1). An organization for general practitioners reported that the topic was not within its main field of expertise. Although part of the representatives answered on paper, we will refer to this part of the study as "Interviews".

Data analysis

Data were analysed by one of the researchers and checked by another researcher. Per theme of the questionnaire, full answers were thematically grouped and gathered in working tables per theme accompanied by a summarizing text. Representatives received this summary and were asked to correct factual mistakes with regard to their country and interview.

**Where to find the results?**

The results of the interviews are used for the identification of specific areas of interest for off-label use in section 4.3, the description of drivers of off-label use in section 4.4, the description of the national frameworks on off-label in section 4.5 and the positions of stakeholders on off-label use in section 4.6. They are also used as input for the analysis of policy options in chapter 5.

2.4.2 Expert meeting

The aim of the expert meeting was to compare positions of Member State representatives and EU-level stakeholders with a clear synthesis of pros and cons. From now on these identified measures and tools will be called policy tools.

Recruitment of participants

Representatives from Member States who are responsible for authorising and controlling the use of the medicinal products, and/or are responsible for pricing and reimbursement, were asked to participate. Also, we invited representatives of EU-level stakeholder organisations (patient organisations, organisations of prescribers and pharmacists and pharmaceutical industry). A total of 30 representatives were invited; 19 persons participated in the meeting (See Table B.2 in Annex B).

Expert meeting

The expert meeting took place March 8, 2016 in Amsterdam, the Netherlands. The meeting started with a presentation of the ongoing study. Subsequently, criteria to assess policy tools in the field of off-label use of medicines were introduced. These were:

- Feasibility of implementation of the policy tool in practice
- Wideness of the scope
- Potential gains
- Potential unintended effects
- Acceptation by healthcare professionals
- Acceptation by patients
- Costs of developing the tool
- Costs of implementation and maintenance of the tool

These criteria were taken in mind when discussing different policy options.

Next, three discussion rounds were held. Each round started with a summary of main policy tools. These tools were discussed and participants could add other tools if they wished to do so. The three rounds were:

- Policy tools at the patient & healthcare professional level;
- Policy tools at the health system level
- Policy tools at the regulatory level.

Outcomes of the discussions were summarized during the last part of the session. The result of the workshop was a set of ideas for policy tools. No recommendations were made with regard to which policy options should be chosen.



Where to find the results?

The results of the expert meeting are mainly used to analyse the pros and cons of a range of policy tools on off-label use (section 4.7). They are also used as input for the analysis of policy options in chapter 5.



3. Legal framework

3.1 Introduction

This chapter describes the legislative frameworks of off-label use. Section 3.2 starts with the broader EU legislation (section 3.2.1). Next, there is a description of the legislation of the regulation of medicinal products where the EU is competent to establish legislation in order to harmonise national legislation in order to safeguard public health and to achieve the goal of a single market for medicinal products (section 3.2.2). The section continues with the use of medicinal products in medical practice (section 3.2.3). This distinction is important as EU legislation does not regulate the way medicinal products are ultimately used in medical practice. The prescribing of a medicinal product, on-label or off-label, is a decision taken within the relationship between a patient and his or her treating healthcare professional (HCP). Section 3.2.4 describes two measures that have been taken in order to encourage research and development of innovative products and to encourage marketing authorisation of medicinal products fulfilling a medical need: the Paediatric Regulation and Orphan Medicinal Product Regulation. Whereas section 3.2 focuses on EU regulation, section 3.3 describes aspects of national legislative frameworks that are important in relation to off-label use. These include regulation on the competencies of healthcare professionals (section 3.3.1), civil law on liability (section 3.3.2), professional and criminal liability and pricing and reimbursement regulation (section 3.3.4). The chapter ends with a section on case law on off-label use both at the EU and the individual Member State level (section 3.4).

This chapter makes use of results from searches in PubMed, Google Scholar and Google; searches in EU and Dutch case law databases, information requests to legal experts with extensive knowledge and experience on pharmaceutical law, the expert meeting, the questionnaire among national experts of EU Member States and EU-level stakeholders (i.e. patients' organisations, healthcare professionals' organisations and pharmaceutical industry), requests to the EPHORT national contacts in Member States, information from DG Santé and a consultation of EMACOLEX.

3.2 EU legislative frameworks

The subsequent section outlines the legal framework relevant for understanding the context of off-label use of medicinal products. The section distinguishes between the regulation of medicinal products and the use of medicinal products in medical practice.

3.2.1 Framework of EU legislation

EU law in general

Strictly speaking, EU law consists of the founding Treaties (primary legislation) and the provisions of instruments enacted by the European institutions by virtue of them (secondary legislation - regulations, directives, etc.). In a broader sense, EU law encompasses all the rules of the EU legal order, including general principles of law, the case law of the Court of Justice of the EU. The single market seeks to guarantee the free movement of goods, capital, services, and people – the "four freedoms" – within



the European Union (EU)^j. The competences of the Union are defined in the EU Treaties^k.

EU competence in the area of public health

Under Article 168 of the TFEU, public health is a competence shared between the EU and Member States. Actions of the EU are restricted to support, coordinate or supplement actions of Member States.^l As a general standard, the definition and implementation of all policies and activities of the EU shall ensure a high level of human health protection.

According to Article 168, paragraph 1, of the TFEU: “A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities. Union action, which shall complement national policies, shall be directed towards improving public health, preventing physical and mental illness and diseases, and obviating sources of danger to physical and mental health. Such action shall cover the fight against the major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education, and monitoring, early warning of and combating serious cross-border threats to health. The Union shall complement the Member States' action in reducing drugs-related health damage, including information and prevention”.^m

Article 168 paragraph 2 of the TFEU provides that *“the Union shall encourage cooperation between the Member States in the areas referred to in this Article and, if necessary, lend support to their action. [...]. Member States shall, in liaison with the Commission, coordinate among themselves their policies and programmes in the areas referred to in paragraph 1. The Commission may, in close contact with the Member States, take any useful initiative to promote such coordination, in particular initiatives aiming at the establishment of guidelines and indicators, the organisation of exchange of best practice, and the preparation of the necessary elements for periodic monitoring and evaluation. The European Parliament shall be kept fully informed”*.

Paragraph 4 of this Article provides that *“the European Parliament and the Council, [...], shall contribute to the achievement of the objectives referred to in this Article through adopting in order to meet common safety concerns: [...]c) measures setting high standards of quality and safety for medicinal products and devices for medical use”*.

And paragraph 7 that *“Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care. The responsibilities of the Member States shall include the management of health services and medical care and the allocation of the resources assigned to them.”*

As a complement to national policies, the actions of the EU shall be directed towards improving public health, preventing physical and mental illness and diseases, and obviating sources of danger to physical and mental health. However, the EU needs to respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care.

^j Art. 26 (2) TFEU.

^k Articles 2-6 of the Treaty on the functioning of the European Union.

^l Art. 4 (2) (k), art. 6 (a) and art. 168 (1) TFEU.

^m Art. 168 (1) TFEU.



Member States are responsible for the management of health services and medical care, including the allocation of resources.ⁿ

The competences of the EU regarding public health are limited by the principle of subsidiarity. In accordance with the principle of subsidiarity, the Union may act only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States, either at central level or at regional and local level, but can rather, by reason of the scale or effects of the proposed action, be better achieved at Union level.^o Moreover, under the principle of proportionality, the content and form of Union action shall not exceed what is necessary to achieve the objectives of the Treaties.^p Once the EU has established legislation, however, Member States are under a duty of sincere cooperation. Member states need to take any appropriate measure to ensure fulfilment of the obligations arising from the legislation, and refrain from any measure which could jeopardise the attainment of its objectives.^q

EU competence in the area of medicinal products

Medicinal products were first regulated on a European level through the establishment of Directive 65/65/EEC, which introduced the requirement of a marketing authorisation for medicinal products. Nowadays Directive 65/65/EEC has been incorporated into the current Directive 2001/83/EC on medicinal products and in Regulation (EC) 76/2004. This EU legislation on medicinal products has been based on article 95 EC (currently article 114 TFEU), referring to the internal market.^r EU medicinal product legislation is based on the harmonisation of national legislation, in order to be able to create free movement of goods in respect of medicinal products. The latter is also reflected in the preambles of Directive 65/65/EEC and the subsequent directives on medicinal products. According to the preamble the primary purpose of any rules concerning the production and distribution of proprietary medicinal products must be to safeguard public health, but this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the EU.^t

In addition, the EU has been provided with a specific competence in the area of medicinal products in article 168 TFEU. For the purpose of improving public health the EU may as a shared competence adopt measures setting high standards of quality and safety for medicinal products (art. 168 (4) (c) TFEU). More recent legislation on medicinal products, such as the pharmacovigilance legislation, refers to both article 114 and 168 TFEU.^u

ⁿ Art. 168 (7) TFEU

^o Art. 5 (3) TEU

^p Art. 5 (4) TFEU

^q Art. 4 (3) TEU

^r Article 95 paragraph 1 EC (currently article 114 TFEU) 1. By way of derogation from Article 94 and save where otherwise provided in this Treaty, the following provisions shall apply for the achievement of the objectives set out in Article 14. The Council shall, acting in accordance with the procedure referred to in Article 251 and after consulting the Economic and Social Committee, adopt the measures for the approximation of the provisions laid down by law, regulation or administrative action in Member States which have as their object the establishment and functioning of the internal market.

^s Regulation (EC) No 726/2004, establishing the centralised procedure and setting up the EMA dealing with veterinary and human medicines is also based article 95 EC (currently article 114 TFEU). In addition, Regulation (EC) 726/2004, is also relates to veterinary issues only, and in that regard is based on Article 152 paragraph 4 under b EC.

^t Recital 1 and 2 of the preamble to Directive 65/65/EEC.

^u Directive 2010/84/EC.



3.2.2 Framework for medicinal products

Medicinal products are extensively regulated in the EU legislation aiming at free movement of goods and the protection of public health. The most relevant secondary legislation with regard to medicines for human use are Directive 2001/83/EC and Regulation (EC) No 726/2004. The legislation regulates the authorisation of medicinal products in the EU by setting common standards of safety, quality and efficacy, and contains rules for, *inter alia*, advertising, package information and distribution of medicines in the EU.

The European Commission, the European Medicines Agency and the Member States are working together in order to assure that all medicinal products for humans put on the European market meet those EU standards on quality, safety and efficacy. For a medicinal product to be placed on the market, it must be authorised by either an EU Member State or by the Commission.

In some cases, “bona fide unsolicited order”^v or “compassionate use”^w, the EU legislation provides for derogations to the marketing authorisation requirements for a medicinal product to be placed on the market.

Directive 2001/83/EC and Regulation (EC) No 726/2004 include four procedures to apply for a marketing authorisation for a medicinal product:

- Centralised procedure: pharmaceutical companies submit a single marketing authorisation application to EMA’s Committee for Medicinal Products for Human Use (CHMP), applying for approval in all EU Member States at once. The EMA operates through its committees by the services offered by the Member States. In this context, the Scientific Committees play an important role. The centralised procedure is compulsory for specific categories of medicines, such as medicinal products manufactured using biotechnological processes, orphan medicinal products and medicines against cancer or diabetes. The majority of innovative products go through this procedure;
- Decentralised procedure: companies can apply for simultaneous authorisation of a medicinal product in more than one EU Member State. This procedure can be used in case a product has not yet been authorised in any EU country and is not mandatory to follow the centralised procedure; one EU Member State is chosen as reference member state and takes the lead in the assessment procedure;
- Mutual recognition procedure: a medicinal product with a national marketing authorisation in one EU Member State can be authorised in other EU countries by mutual recognition of this first authorisation in one or several other EU countries; the Member State of first authorisation acts as reference member state and provides the assessment report;
- National procedure: medicinal products can also apply for a marketing authorisation in one EU member state; this results in strictly a national authorisation.

The decision to grant or refuse a marketing authorisation is based on an assessment (by the competent authorities) of the quality, safety and efficacy of the medicinal product, and of the benefit/risk ratio. This assessment is conducted on the basis of chemical-pharmaceutical, clinical and preclinical data submitted to the authorities. In general, the assessment of the benefit/risk ratio focuses on a specific condition in a specific subpopulation, investigated in clinical trials. A beneficial and clinically relevant

^v Article 5 of Directive 2001/83/EC.

^w Article 83 of Regulation 726/2004, CHMP Guideline on compassionate use of medicinal products, pursuant to Article 83 of regulation (EC) No 726/2004.



outcome of the product found in (the subpopulations included in) these trials constitutes the basis to grant a marketing authorisation for a medicinal product. Which indications and subpopulations are investigated is up to the applicant. Consequently, the regulation of medicinal products is based on information about populations of patients using a specific medicinal product, rather than on individual patients' characteristics.

The requirements for obtaining a marketing authorisation are explicitly set out in the applicable legal framework of medicinal products. According to article 6 (1) Directive 2001/83/EC it is in principle prohibited to market medicinal products without a marketing authorisation.^x The exemptions to the requirement of a marketing authorisation are limited in number and subject to multiple conditions. The exemptions include magisterial^y and officinal formulae^z, medicinal products in authorised clinical trials^{aa}, medicinal products in medical need situations (named patient supply^{bb}, emergency situations^{cc} and compassionate use programs^{dd}). In accordance with settled case-law, generally provisions which are in the nature of exceptions to a principle must be interpreted strictly.^{ee} Consequently, (a number of) the exemptions have been further delimited in their scope by the Court of Justice of the European Union's (CJEU) interpretation in a number of court cases that are of particular interest.

The case *Commission v Poland* concerned the exemption for named patient supply in article 5 (1) of Directive 2001/83/EC.^{ff} Article 5 (1) allows a Member State to, *"in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility"*. The court considered that the application *"must remain exceptional in order to preserve the practical effect of the marketing authorisation procedure"*^{gg} and that it should only be used *"if that is necessary, taking account of the specific needs of patients."*^{hh} Accordingly the court provided the following interpretation of 'special need' and a 'bona fide unsolicited order' in article 5 (1). The concept of 'special needs' *"applies only to individual situations justified by medical considerations and presupposes that the medicinal product is necessary to meet the needs of the patient."*ⁱⁱ A 'bona fide unsolicited order' means that *"the medicinal product must have been prescribed by the doctor as a result of an actual examination of his patients and on the basis of purely therapeutic considerations."*^{jj} Moreover, the court considered that article 5(1) *"can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market."*^{kk} The court also stressed that no special need exists if there are already authorised medicinal products available on the national

^x Article 6 (1) Directive 2001/83/EC.

^y Article 3 (1) Directive 2001/83/EC.

^z Article 3 (2) Directive 2001/83/EC.

^{aa} Article 3 (3) Directive 2001/83/EC.

^{bb} Article 5 (1) Directive 2001/83/EC.

^{cc} Article 5 (1) Directive 2001/83/EC.

^{dd} Article 83 Regulation (EC) nr. 726/2004.

^{ee} Joint cases C-544/13 and C-545/13 *Abcur v Apoteket* [2015], paragraph 53 and 54.

^{ff} C-185/10 *Commission v Poland* [2012], JGR 2012/14 with commentary from M.D.B. Schutjens.

^{gg} C-185/10 *Commission v Poland* [2012], paragraph 32 and 48.

^{hh} C-185/10 *Commission v Poland* [2012], paragraph 33.

ⁱⁱ C-185/10 *Commission v Poland* [2012], paragraph 34.

^{jj} C-185/10 *Commission v Poland* [2012], paragraph 35.

^{kk} C-185/10 *Commission v Poland* [2012], paragraph 36.



market with the same active substances, the same dosage and the same form.^{ll} The court emphasized that financial considerations do not lead to a special need.^{mmm} So, financial consideration cannot justify an exemption from the requirement for a marketing authorisation.

The CJEU's ruling in the case *Novartis v Apozyt* concerned the interpretation of Article 3(1) of Regulation (EC) No 726/2004. The request for a preliminary ruling was made in proceedings between Novartis Pharma GmbH ('Novartis') and Apozyt GmbH ('Apozyt') concerning whether Apozyt may produce, distribute and promote ready-to-use syringes that are intended for the treatment of eye disease and contain doses of the medicinal products Lucentis and Avastin. The referring court asks, in essence, whether activities such as those at stake in the proceedings require a marketing authorisation under Article 3 (1) of Regulation (EC) No 726/2004,ⁿⁿ which determines the scope of products eligible to the centralised procedure and, if not, whether these activities remain subject to Directive 2001/83.

Apozyt prepared, using the content of Novartis' medicinal products Lucentis (Ranibizumab) and Roche's Avastin (Bevacizumab), pre-filled syringes with the exact amount as prescribed by physicians. The pre-filled syringes were delivered to pharmacies, which had ordered the syringe on prescription for a patient. The Apozyt's method allowed the vials of Lucentis and Avastin to be used for multiple injections and at a lower price than Lucentis and Avastin. Novartis and Apozyt disagreed about whether Apozyt's syringes required a new marketing authorisation.^{oo}

The answer to the question was that activities such as those in the main proceedings, provided that they do not result in a modification of the medicinal product concerned and are carried out solely on the basis of individual prescriptions calling for processes of such a kind – a matter which is to be determined by the referring court –, do not require a marketing authorisation under Article 3(1) of Regulation No 726/2004 but remain, in any event, subject to Directive 2001/83.

In particular, the court determined that the activity of Apozyt cannot *"be equated with a new placing on the market of a medicinal product"*,^{pp} and accordingly, Apozyt *"in that respect, [is] not subject to the obligation to hold a marketing authorisation (...)"*,^{qq} provided *"that the processes in question do not result in any modification of the medicinal product and that they are carried out solely on the basis of individual prescriptions making provision for them"*.^{rr}

The court also considered that *"the activity carried out by a company such as Apozyt occurs after the medicinal products at issue in the main proceedings have been placed on the market. In particular, the drawing off of liquid medicinal products from the original vials, and the transfer into ready-to-use syringes of the portions so drawn off, without any modification of those products, is in reality analogous to actions which, in the absence of Apozyt's activities, could otherwise be, or have been, carried out,*

^{ll} C-185/10 *Commission v Poland* [2012], paragraph 37.

^{mmm} C-185/10 *Commission v Poland* [2012], paragraph 38. Cf. C-459/00 P(R) *Commission v Trenker* 2001 I-02823, paragraph 109 regarding the precedence of protection of public health over economic considerations.

ⁿⁿ C-535/11 *Novartis v Apozyt* [2013].

^{oo} C-535/11 *Novartis v Apozyt* [2013].

^{pp} C-535/11 *Novartis v Apozyt* [2013], paragraph 42.

^{qq} C-535/11 *Novartis v Apozyt* [2013], paragraph 42.

^{rr} C-535/11 *Novartis v Apozyt* [2013], paragraph 42.



under their responsibility, by doctors prescribing the treatment or by pharmacies themselves in their dispensaries, or else in hospitals.^{ss}

3.2.3 Use of medicinal products

Whereas market approval of medicinal products is the subject of EU legislation, the use of medicinal products in medical practice (e.g. prescription at individual level) is not. The marketing authorisation holder (i.e. the pharmaceutical company) and the regulators are responsible for (assessing) the quality, efficacy and safety of a medicinal product. However, the actual prescribing is a decision taken in the relationship between a patient and his or her treating HCP. The way Member States organise their healthcare system and the way HCPs conduct their practice is not a topic that falls within the remit of the EU. Following the subsidiarity principle, laid down in Article 5 of the TEU and Protocol (No. 2) on the principles of subsidiarity and proportionality, the authority on the organisation and the conduct of healthcare remains with the Member States. This includes off-label use of medicinal products. The latter has recently been acknowledged by the General Court that stated *“In the EU, off-label prescribing is not prohibited, or even regulated by law. There is no provision [in EU law] which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted.”*^{tt}

Directive 2010/84/EU states that marketing authorisation holders (MAHs) are responsible to provide all available information on their products, including the results of clinical trials or other studies as well as any use of the product outside the terms of its marketing authorisation (i.e. off-label use). Prior to enactment of Directive 2010/84/EC *soft law* (i.e. the guidance document on pharmacovigilance) already established an obligation to provide information for uses outside the terms of the marketing authorisation.^{uu} Directive 2010/84/EC codified that obligation in EU legislation. Also, the preamble to Directive 2010/84/EC states that Member States should operate pharmacovigilance systems to collect information that is useful for the monitoring of medicinal products. This includes information on suspected adverse reactions as a result of the use of a medicinal product, also in case this use was off-label.

“Member States should operate a pharmacovigilance system to collect information that is useful for the monitoring of medicinal products, including information on suspected adverse reactions arising from use of a medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation [...].”^{vv}

The amended pharmacovigilance legislation also stresses the importance of providing patients with possibilities to report suspected adverse drug reaction, including those of off-label use.^{ww} Post authorisation studies may be aimed at collecting data to enable the assessment of the safety or efficacy of medicinal products in everyday medical practice.^{xx}

^{ss} C-535/11 *Novartis v Apozyt* [2013], paragraph 43.

^{tt} General Court, case T-452/14 *Laboratoires CTRS v Commission* [2015].

^{uu} P. 82, 196. Volume 9A of the Rules governing medicinal products in the EU. Available from http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf

^{vv} Recital 17 of the preambles to Directive 2010/84/EC.

^{ww} Recital 21 of the preambles to Directive 2010/84/EC.

^{xx} Recital 9 of the preambles to Directive 2010/84/EC.



Moreover, it should be stressed that off-label use is subject to legislation that is not specific for medicinal products, or even for medical practice. Liability for off-label prescribing, for example, is governed by liability legislation dealing with both (EU) product liability and professional liability. Off-label as well as on-label prescriptions can be inappropriate, which (may) lead to liability. Furthermore, the prescriber and other healthcare professionals have to comply with ethical and professional standards. Compliance with ethical and professional standards is monitored by disciplinary boards and committees. Moreover, whether off-label use of a medicinal product is reimbursed depends on the national health insurance legislation. In some member states the reimbursement of some medicinal products is limited to authorised uses. Finally, criminal law applies also to the work of healthcare professionals. These elements show that off-label use is governed by some Member States' national laws, although not in a systematic manner. Section 3.3 will deal with these aspects in more detail.

3.2.4 Paediatric Regulation and Orphan Medicinal Product Regulation

In order to encourage research and development of innovative products and to encourage marketing authorisation of medicinal products fulfilling a medical need, several measures have been taken at EU-level.

Paediatric Regulation

A first example is the introduction of Regulation (EC) No 1901/2006/EC, known as the Paediatric Regulation. This was seen as a response to the absence of sufficient numbers of suitable, authorised medicinal products for children. The regulation was adopted in 2006 to *"ensure that medicines are regularly researched, developed and authorised to meet the therapeutic needs of children"*^{yy}. Its objectives were to:

- facilitate the development and availability of medicines for paediatric use;
- ensure that medicinal products for use for the treatment of children are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population;
- improve the available information on the use of medicines in various paediatric populations.^{yy}

One measure was to require companies to submit data on the use of a medicine in children in accordance with an agreed paediatric investigation plan (PIP) when applying for marketing authorisation. This PIP is assessed by the Paediatric Committee (PDCO).⁶ The PDCO judges the PIPs on the measures proposed by the applicant to demonstrate the quality, safety and efficacy of the medicines in one or more specified paediatric populations. When applying for marketing authorisation for a new product or for a new indication, pharmaceutical form or route to be authorized in children, the completion of the PIP needs to be demonstrated. When the studies of the agreed PIP are completed and the medicinal product authorised, there are rewards. Examples are a six months extension of the supplementary protection certificate (including adult use) and, in case of orphan drugs, the market exclusivity is extended from 10 to 12 years.

Pharmaceutical companies can, according to Article 30 of Regulation (EC) No 1901/2006 ("Paediatric Regulation"), also apply for a paediatric use marketing authorisation (PUMA). The PUMA is defined as "a dedicated marketing authorisation for medicinal products indicated exclusively for use in the paediatric population (or subsets thereof) not covered by intellectual property rights, with, if necessary, an age-

^{yy} Regulation (EC) No 1901/2006,
<http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32006R0901>



appropriate formulation".^{zz} The major incentive for applying for a PUMA is that it benefits from 8 years of data protection and 2 additional years of market protection (Article 38 of the Paediatric Regulation). Other incentives are:^{aaa}:

- PUMA applications have 'automatic access' to the centralised procedure (Article 31 of the Paediatric Regulation);
- A medicinal product for which a PUMA has been granted may retain the name of another medicinal product containing the same active substance for which the same holder has been granted an authorisation for use in adults (Article 30(4) of the Paediatric Regulation);
- PUMA applications submitted under the centralised procedure benefit from a partial exemption from the payment of the fees laid down in the Regulation (EC) No 297/95.

Orphan Medicinal Product Regulation

Another area where the EU has introduced incentives in the legislation is medicines for rare diseases: the Orphan Medicinal Product Regulation (EC) No 141/2000/EC, which entered into force in 2000. Again, this regulation was designed to stimulate pharmaceutical companies to develop new medicinal products for a particular patient group, in this case those with a rare disease (affecting five or less per 10,000 patients in the EU). Moreover, also MAHs can apply for an orphan designation for new indications of an already authorised product (that might already be used off-label for that new indication). One measure was the establishment of the Committee for Orphan Medicinal Products (COMP), which is responsible for all EU orphan drugs applications for designation by pharmaceutical companies. In order to obtain an orphan drug designation, pharmaceutical companies have to demonstrate in their application that their medicinal product:

- is intended for the diagnosis, prevention or treatment of life threatening or seriously debilitating condition affecting not more than 5 patients per 10,000 inhabitant or that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment

AND

- that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.^{bbb}

Application for orphan designation must be made before the application for the marketing authorisation is made. When a medicinal product receives an orphan designation it is entered into the Community Register of Orphan Medicinal Products of the EC. Once the pharmaceutical company applies for marketing authorisation, the Committee for Medicinal Products for Human Use (CHMP) adopts an opinion about the quality, safety and efficacy of the orphan medicinal product, and the risk/benefit ratio. The COMP is also asked to confirm whether the orphan designation criteria are still met at the time of the marketing authorisation. The EC makes the final decision for market approval. The main incentive for companies to apply for an orphan designation is the 10 year- market exclusivity for the orphan medicinal product. Other incentives are protocol assistance (scientific advice regarding the necessary trials to show quality, safety and efficacy); fee waivers; funded research (grants for research from Member States and community) and access to the centralized procedure of the EMA.⁷

^{zz} http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/09/WC500112071.pdf

^{aaa} Literally cited from http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/09/WC500112071.pdf

^{bbb} http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf



3.3 National frameworks

3.3.1 General

In all EU Member States the competencies of healthcare professionals – what they are allowed to do and what they are not allowed to do – have been laid down in either public professional legislation, concerning the practicing of healthcare professions or in laws on the treatment agreement between healthcare professionals and/or healthcare institutions and their patients. These national legislations contain provisions about the obligation of any healthcare professional to treat patients to the best of his/her ability and only after patient's consent based upon full information about possible benefits and risks, alternative treatments and predictions of what will happen if the patient decides against a treatment. Furthermore, such national laws contain provisions in respect of professional secrecy, and dealing with professionally privileged data. Within these national legislative systems, the patients' rights that may be derived from international agreements, like the Council of Europe conventions and guidelines offered by the World Medical Association, have to be reflected. These national legislations should also be in line with the Council Conclusions on Common values and principles in the European Health systems.^{ccc}

A specific aspect of the treatment of patients is the prescribing of medicinal products. This concerns in general a competence reserved for specific types of healthcare professionals, such as physicians, dentists, midwives and specialised nurses (for medicinal products they use in their practice). Generally, the professional legislation does not limit the right to prescribe to on-label prescription, as this would in many cases lead to a conflict of duties: the prescriber wants to propose the best possible treatment even if that treatment is off-label. This view was supported by the interviews that were held within the context of this study. Many interviewees from different backgrounds (regulators, payers, patients, HCPs, industry) mentioned that off-label use is an issue that should be dealt with in the context of the prescriber-patient relation as prescribers know what is best for the well-being of the patient (see also section 3.3).

In the individual relationship between a healthcare professional and his or her patient everything turns around the individual result of the treatment. Therefore, the outcome of the treatment is more important than the regulatory status of the treatment and the concept of appropriateness is important. The scientific literature suggests that any prescription should reflect the best possible care, irrespective of the on- or off-label status.^{ddd} In case of off-label prescription, the prescriber has to weigh the benefit/risk ratio, whereas in the case of on-label prescription, competent authorities have evaluated the benefit/risk ratio. On the other hand, not to treat a patient off-label may be against a healthcare professional's obligations to provide the best possible care. Literature also suggests that in case of off-label prescribing the informed consent should be in written form, for example in case an unforeseen incident.^{eee}

^{ccc} Adopted on 1 June 2006: Council Conclusions on Common Values and Principles in European Union Health Systems [http://eur-lex.europa.eu/legal-content/en/txt/?uri=CELEX:52006XG0622\(01\)](http://eur-lex.europa.eu/legal-content/en/txt/?uri=CELEX:52006XG0622(01)).

^{ddd} E.g. V. Henry, 'Off-Label Prescribing', *The Journal of Legal Medicine* 1999, p. 365-383 (p. 369)

^{eee} See e.g. Carla Schoonderbeek, John Lisman, *Off-label use of medicinal products: a legal update*; PLC Cross-border Handbook, Life sciences 2007/2008; p. 25 – 31, referring to Dutch case law about appropriate off-label use for which the prescriber was sanctioned anyway, because he did not inform his patient (Centraal Medisch tuchtcollege, 10-02-1998, no ECLI or case number available, published in *Jurisprudentie Geneesmiddelenrecht*, JGR 2007/42).



3.3.2 Civil law Liability

A patient's medical treatment may fail or a patient may experience adverse effects from the applied medicinal products. If so, the issue of liability arises. A HCP can be held accountable for mistakes that have a negative impact on the patient's health. Although the HCP is responsible for the treatment of the patient, he/she cannot be held liable for any negative effect of for example the treatment with a medicinal product. Treatment with a medicinal product can always have unexpected or undesired effects: all medicinal products have associated risks of adverse drug reactions. Moreover, medicinal products are tested in populations that cannot predict the actual efficacy and safety in an individual.

The risk that a court or judge will accept liability of a HCP in case of off-label prescribing is slightly higher than in case of on-label prescribing. However, if the off-label treatment is considered appropriate,^{fff} the prescriber will not automatically be deemed liable for damages. In fact, there is not so much of a difference between off-label and on-label prescribing when it comes to matters of liability. The main difference between off-label and on-label prescribing with regard to liability is the fact that for on-label prescribing the HCP can rely on the evaluation of the product by the competent authorities, while for off-label use he cannot. If a HCP is held liable for the outcome of a medical treatment, the approval by the competent authorities is a strong defence. If a HCP is held liable for off-label use that is mentioned in a professional guideline, this is, although somewhat weaker, normally a convincing defence. Just in cases where the HCP cannot convince the court or judge of the rationality and appropriateness of the off-label prescription the professional and/or his or her insurance company might have to pay damages.

The marketing authorisation holder's perspective on liability is slightly different. If there is an incident with regard to a medicinal product, the Product Liability Directive (Directive 85/374/EEC) applies. This directive draws complete liability to the manufacturer of a defective product, including the burden of proof. However, the marketing authorisation holder can avail of important defences. Expectable adverse events do not make a medicinal product defective: they belong to the normal risk of using a medicinal product. Another strong defence for pharmaceutical industry is the claim that a product, that in itself is not defective, was used wrongly. If the off-label use is well-established, however, this defence might not be strong enough.

3.3.3 Professional and criminal liability

In extreme cases, inappropriate off-label use could lead to complaints about the prescriber's misconduct and to an inquiry by a disciplinary board or even to criminal charges. Such off-label use is not discussed in this report, because it is rather distanced from normal medical practice.

3.3.4 Pricing and reimbursement legislation

In line with Article 168 (7) TFEU, systems for pricing and reimbursement of medicinal products are the competence of Member States (as also is the case for the organisation of healthcare).⁹⁹⁹ This has been acknowledged in Directive

^{fff} The concept of appropriate off-label use was developed in: M. Gazarian, M. Kelly, J.R. McPhee, L.V. Graudins, R.L. Ward & T.J. Campbell, 'Off-label use of medicines: consensus recommendations for evaluating appropriateness', MJA2006, p. 544-548.

⁹⁹⁹ Art. 168 (7) TFEU.



2001/83/EC,^{hhh} as well as in Regulation (EC) No 726/2004. Article 4(3) of the Directive explicitly states that the provisions of Directive 2001/83/EC shall not affect the powers of the Member States' authorities either with regard to the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.ⁱⁱⁱ Moreover, in accordance with settled case-law EU law does not detract from the power of the Member States to organise their social security systems.^{jjj}

The only Union legislation about pricing and reimbursement of medicinal products is the so-called Transparency Directive 89/105/EEC, providing Member States with a set of rules about the transparency of their decision-making, maximum decision terms and guarantees for the free movement of goods. In relation to the latter, a Member State may not treat pharmaceutical companies different if they are located in a different Member State or on their own territory. The requirements by the Transparency Directive are intended to ensure that all concerned can verify that the national measures do not constitute quantitative restrictions on imports or exports or measures having equivalent effect.^{kkk}

Within the national pricing and reimbursement systems, Member States may have established a wide variety of rules that limit reimbursement of medicinal product in off-label uses as well as in on-label uses.

3.4 Case law

Part of this study was dedicated to research into case law of the EU and the national courts, relevant in respect of off-label use. As stated before, the off-label prescribing of medicines is not regulated by EU legislation. The EU legislation does not regulate the use of medicines for indications other than included in the SmPc. It does not intend to regulate the way the products are ultimately used in medical practice. This means that there is a limited amount of relevant case law, both in the EU courts, and in national courts. All court cases that were collected via searches in relevant databases, legal experts, experts in the field of off-label use and interviewees in EU Member States (see section 2.2 for more information) were analysed on relevance for off-label use and, if relevant, on the outcomes.

The way HCPs fulfil their tasks is not within the EU remit, but rather remains within the competence of the member states. The CJEU primarily confirmed that off-label use as such is not regulated by EU law and EU law does not prohibit physicians to apply medicinal products off-label. In various other cases the CJEU reflected on the marketing authorisation system as established in the EU legislation and the powers of the European Commission in regulating medicinal products. Such court cases are distantly of interest to off-label use. For example, the court has addressed the doctrine of the precautionary principle in the case of Pfizer Animal Health and the power of the European Commission to withdraw or suspend a marketing authorisation in the case of Artergolan.

^{hhh} Article 4 (3) of Directive 2001/83/EC:

ⁱⁱⁱ Article 1 (2) of Regulation (EC) No 726/2004 is almost identical to article 4 (3) of Directive 2001/83/EC and states: the provisions of this Regulation shall not affect the powers of Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions. In particular, Member States shall be free to choose from the particulars shown in the marketing authorisation those therapeutic indications and pack sizes which will be covered by their social security bodies.

^{jjj} CJEU 12 July 2001 (Smits Peerbooms), C-157/99, ECLI:EU:C:2001:404, par. 44.

^{kkk} Recital 6 of the preamble to Directive 89/105/EEC.



During the analysis, it appeared that part of the court cases are not more than indirectly of interest for policies on off-label use. The analysis provided insight into the reasons why these cases are only of indirect relevance for off-label use.

In *European Commission v Republic of Poland* the CJEU clarified the meaning of article 5 (1) of Directive 2001/83 and emphasised that the exemption to the marketing authorisation requirement in article 5 (1), also known as named-patient use, cannot be applied just for financial considerations. In *Novartis Pharma v Apozyt* the court established that certain activities related to a licensed medicinal product may be performed without the need to apply for a (new) marketing authorisation.

The cases of the CJEU may be taken into account in the assessment of the lawfulness of any (future) EU or national policy on off-label use; even though the court cases are only indirectly related to off-label use. National court cases about off-label use relate to a large extent to reimbursement. These cases indicate that additional requirements to reimbursement may apply, including the limitation to life-threatening or severe conditions and the absence of alternative treatment options. Other national court cases concern the (professional) liability prescribing or dispensing medicinal products off-label.



4. Extent of off-label use and current practices

4.1 Introduction

This chapter presents information gathered on different aspects of off-label use and contains results as presented in the literature, from interviews and from the expert meeting. In order to provide a picture of the scope of the problem of off-label use, this chapter starts with an overview of the literature on the extent of off-label use in children and adults in EU Member States (section 4.2). Not only the extent of off-label use is an important factor to capture, but so is the question whether there are therapeutic areas, specific patient groups and specific situations for therapeutic use that are more prone to off-label use of medicinal products. These areas are described in section 4.3. After exploring the extent of and important areas for off-label use are known, we describe what drives this off-label use: what factors make that off-label use exists and when is it more likely to occur? We thereby focus on drivers at different levels: the patient and HCP level, the health care system level and the regulatory level (section 4.4). Off-label use takes place within the health care systems and regulatory settings of the EU Member States. EU Member States can take actions to influence the extent and nature of off-label use. Section 4.5 therefore describes which practices are in place with regard to off-label use in EU Member States and whether or not there are new measures in preparation. These measures might be of value for other Member States as well. However, there are several stakeholders involved in off-label use and their opinions may have an impact on the acceptance of measures for off-label use. Therefore, we assessed both the opinions of stakeholders on off-label use in general (section 4.6) as well as on the pros and cons of different measures in the field of off-label use (section 4.7).

This chapter is merely a description of the results from the different data collections performed within the context of the study. As we wanted to describe the wide variety of opinions and ideas, also statements made by individual respondents are included in this chapter. At the end of sections where different opinions on off-label use are discussed a sub-section is devoted to an overview of the opinions of different stakeholders. Here, we combined the views of stakeholders in the regulatory and reimbursement field as these were often combined in one person or within a group response to our questions. The large majority of the interviewed persons at the national level were in the regulatory field.

The information in chapter this was collected in order to be able to make a factual analysis of off-label use and practices in the EU Member States (including national legislation and case law where relevant) against the EU legal framework, and to identify particular aspects and/or therapeutic areas of off-label use that would deserve specific attention at EU level. The analysis is presented in chapter 5.



4.2 Extent of off-label use in EU Member States

Key findings on the extent of off-label use

Children

- 32 studies on off-label use (including data from 16 EU Member States) in various paediatric populations in the hospital setting showed a range of 13-69% of the investigated prescriptions being off-label. In 40 studies (including data from 12 Member States) in the outpatient setting, a wider range of 2-100% was found.
- Variation in off-label prevalence is not only observed between but also within countries, depending for example on the methodology used and the population studied.
- So far, the introduction of the Paediatric Regulation (1901/2006/EC) does not seem to have led to a lower prevalence of off-label use.

Adults

- 23 studies on off-label use (including data from 6 EU Member States) in various adult populations in the inpatient setting showed a range of 7-95% of the investigated prescriptions being off-label. In 13 studies (including data from 6 Member States) in the outpatient setting a range of 6-72% was found.

4.2.1 Prevalence in children

The development of medicines for children is associated with a number of challenges including high costs, a small and highly fragmented market and methodologic and ethical requirements for paediatric trials⁴. As a result, only limited research has been done to adapt medicines for the needs of the paediatric population and many medicines that are on the market have not been tested in children in the pre-registration phase. In the period between 1995 and 2005 one-third of all medicines assessed by the EMA were authorised for use in children⁴. Moreover, especially in younger children and neonates, authorized paediatric medicines may not always be age appropriate for example with respect to dosing and suitability of dosage forms. To stimulate the authorisation of medicines for children in the EU, regulation 1901/2006/EC (Paediatric Regulation) became effective in 2007. This regulation "establishes a system of obligations, rewards and incentives, together with horizontal measures to ensure that medicines are regularly researched, developed and authorised to meet the therapeutic needs of children"⁸.

The systematic literature review of the literature (see section 2.3 for a description of the methods) shows that off-label use in children exists in EU Member States. Below the main results are described. Annex E provides more detailed information on each study included as well as the exact literature references. All prevalence figures are expressed as the percentage of the total number of prescriptions prescribed to the population under study, unless otherwise stated. So, if a study on children in the hospital reports a percentage of 33% this means that 33% of the total number of the prescriptions investigated in that particular study population was an off-label prescription. In case a study included an overall prevalence as well as prevalence figures for subgroups, only the overall prevalence is included in the figures in this section. Annex E also includes the subgroup information. In case a study did not provide an overall prevalence figure, but only showed information per subgroup, the



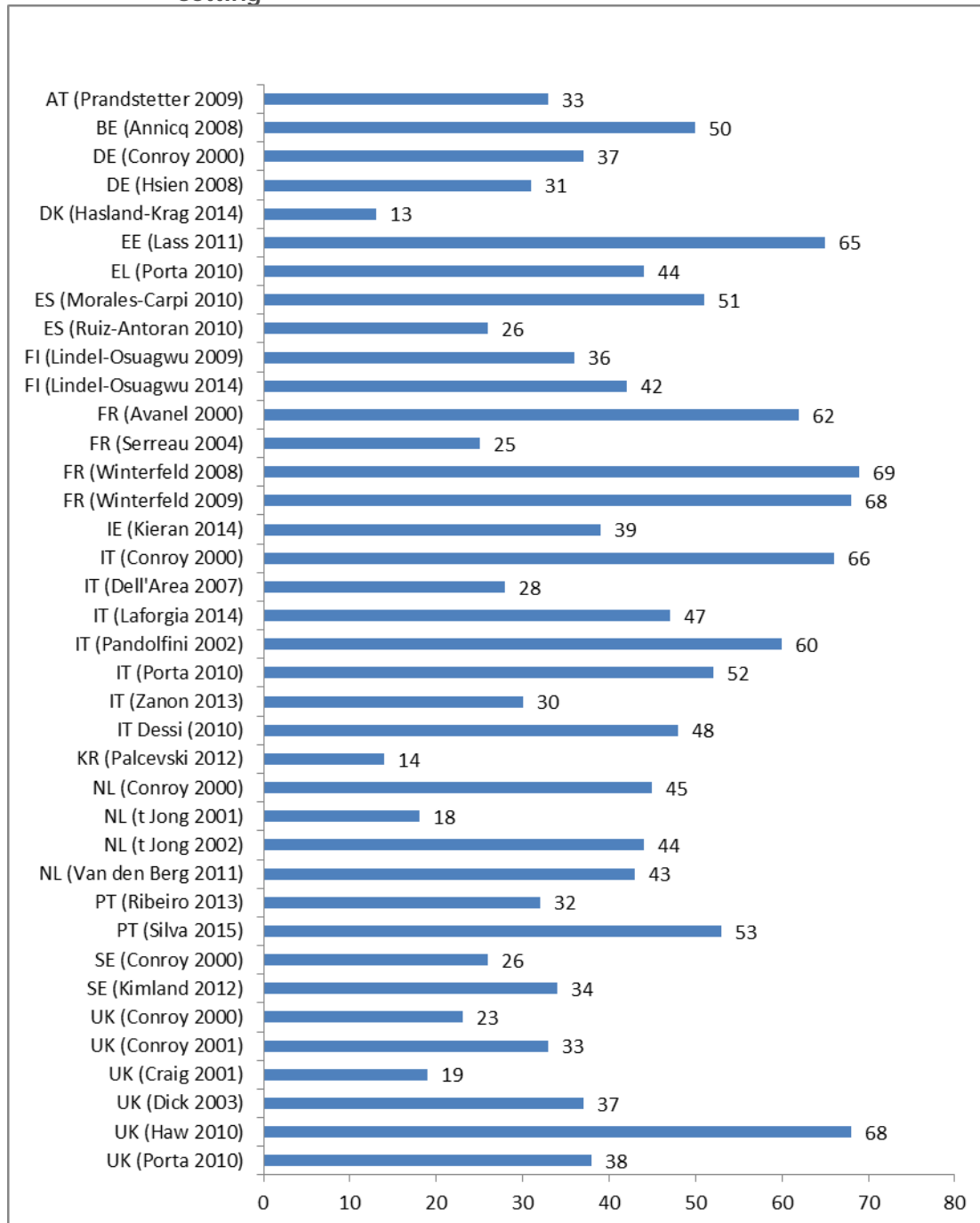
highest prevalence was included in the figures in this section; all other figures are shown in Annex E.

Figure 4.1 includes the prevalence figures of 32 studies that were performed in the hospital setting. These studies provide figures from 16 EU Member States. Thirty studies covered one Member State. The other two studies covered multiple Member States. Overall, the figures show that off-label use is common in children in the hospital setting across the EU. Figure 4.1 also shows that there is a large variation in the percentage of off-label prescriptions in children with 13% as lowest prevalence and 69% as highest. This variation is not only observed across Europe, but also within countries. Reasons for this variation are methodological (the way off-label use is measured), the area for which off-label use is measured (indication, dosing etc.) and the patient selection. However, no clear patterns (for example more off-label use in certain diseases) could be observed. The range for the outpatient setting seems to be even wider as is shown from results of 40 studies providing figures from 12 EU Member States (2%-100%; Figure 4.2). Again, large variation within countries is observed, but no clear patterns were identified (for example more off-label use in certain diseases).

Some studies in the systematic literature review focus on HCPs and the question whether or not they prescribe off-label. Table 4.1 shows that a large proportion of paediatricians, child psychiatrists and neonatologists prescribe off-label according to their self-reporting in questionnaires. Looking at the years these surveys were conducted, it appears that the prevalence of off-label use in children is still very pertinent after introduction of the Paediatric Regulation.



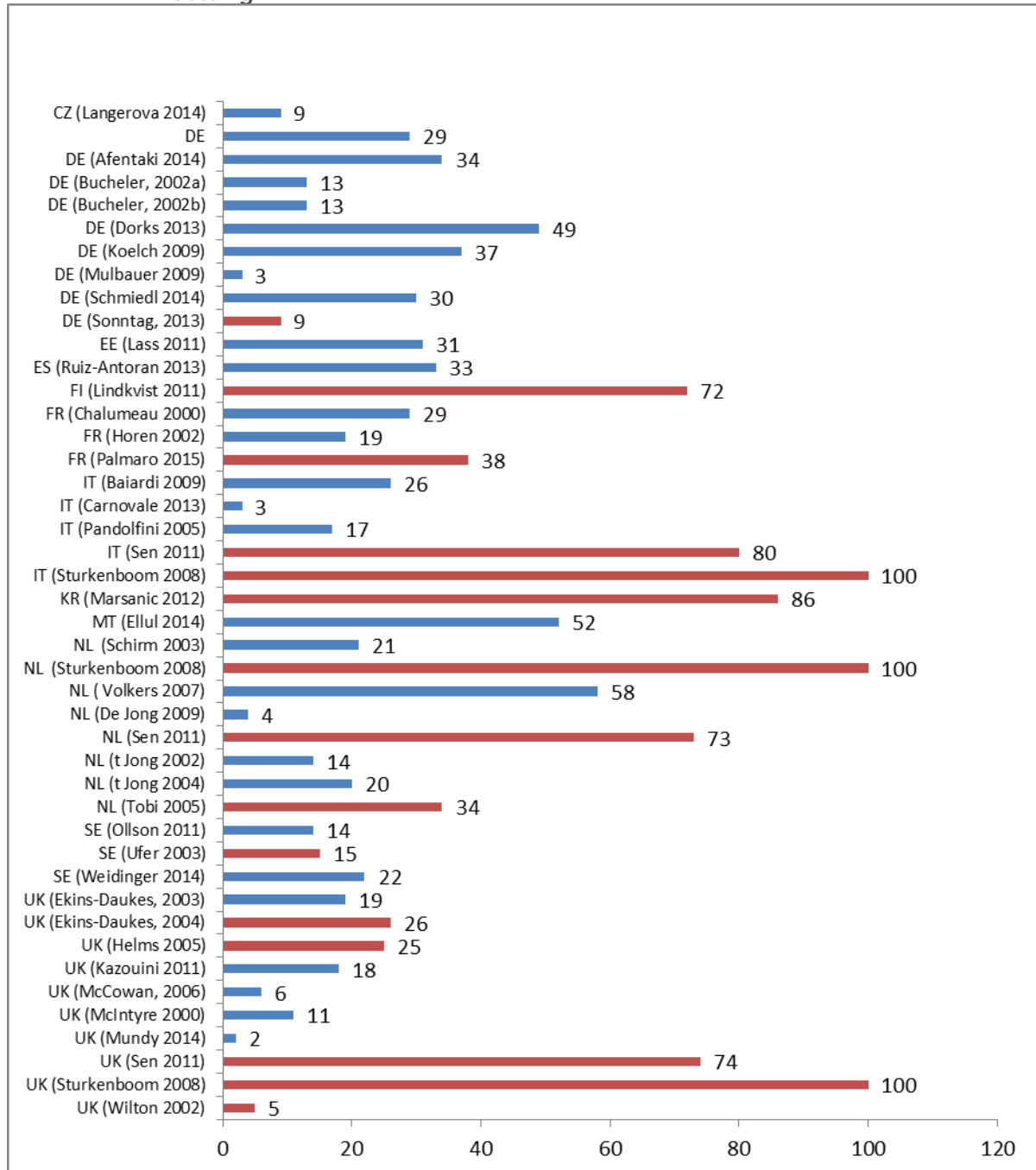
Figure 4.1 Prevalence of off-label use in children; data obtained in the hospital setting



All prevalence figures are expressed as percentage of the total number of prescriptions investigated in the study reported in literature. So, 33% means that 33% of the total number of prescriptions investigated in that particular study was off-label. Some studies did not provide an overall off-label figure, but prevalence figures per disease area / indication or per ATC-class / drug substance. In that case, the highest figure is shown. For a detailed overview of all studies and prevalence figures for children, reference is made to Annex E.



Figure 4.2 Prevalence of off-label use in children; data obtained in the outpatient setting



The figures in the red bars are expressed as percentage of all children included in the study. All other figures are expressed as percentage of the total number of prescriptions investigated in that particular study. Some studies did not provide an overall off-label figure, but prevalence figures per disease area / indication or per ATC-class / drug substance. In that case, the highest figure is shown (which resulted for three studies in depicting 100% as prevalence figure, while actually a range of 0-100% was found, depending on the disease area). The data outside the hospital were in most cases (>85% of all studies included) retrieved from pharmacy dispensing databases, prescription databases, health insurance databases or (electronic) medical records. For a detailed overview of all studies and prevalence figures for children, reference is made to Annex E.


Table 4.1 Prevalence of off-label prescribing at HCP level

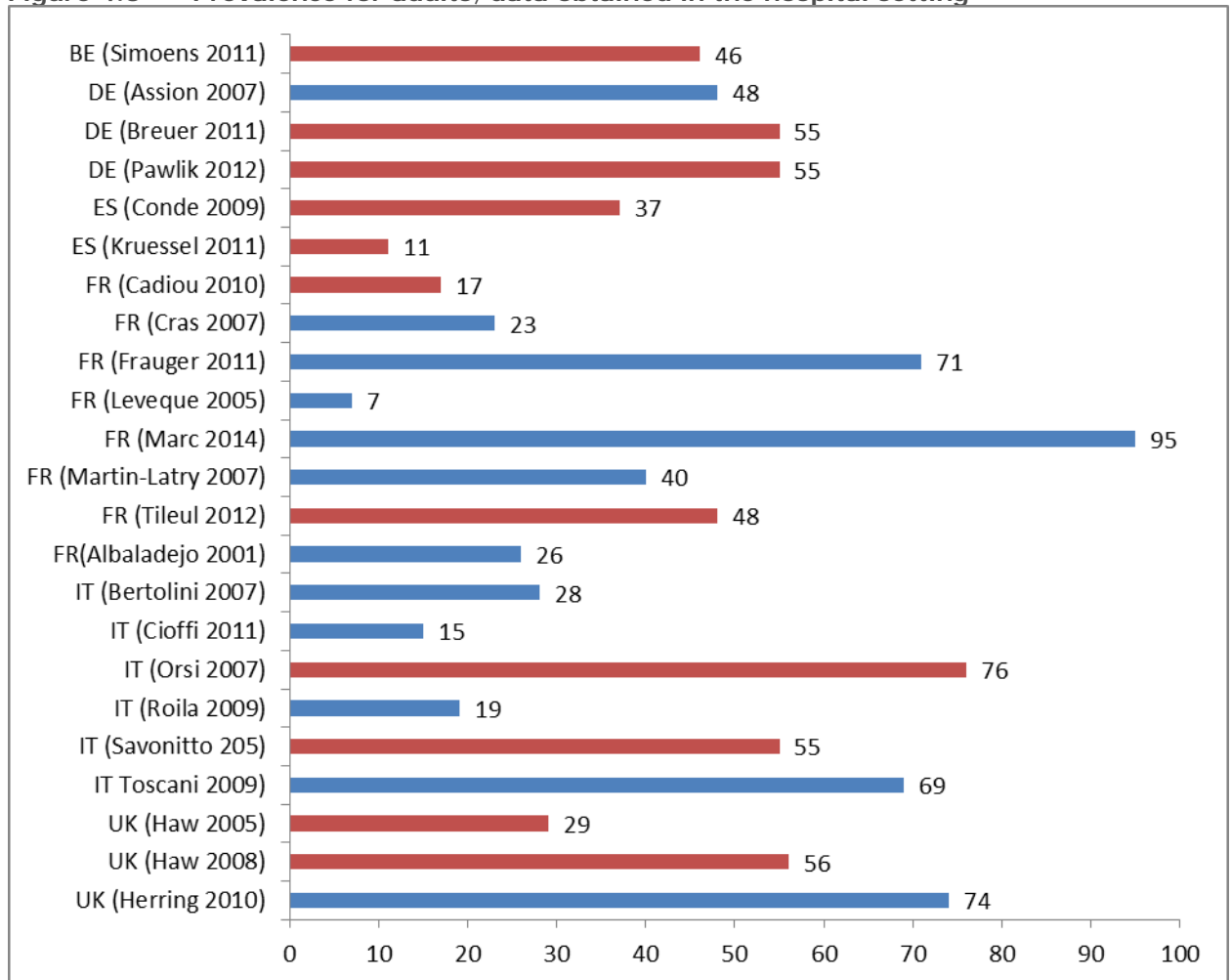
	Percentage of hospitals / departments / units	Percentage of physicians	Specialist / specialism
DE (Kruessel 2012)	79		Paediatric intensive care units
DE (Koppelstaetter 2011)	46		Neonatology, paediatric neurology
NL (Hugtenburg 2005)		71	Child psychiatrists
NL (Jochemsen 2009)		100	General practitioners*
PL (Kuchar 2010)		57	Paediatricians
UK (Hodgson, 2000)		65	Psychiatrists
UK (Stewart 2007)		40	Paediatricians
UK (McLay 2006)		90	Paediatricians

* Refers to children and adults.

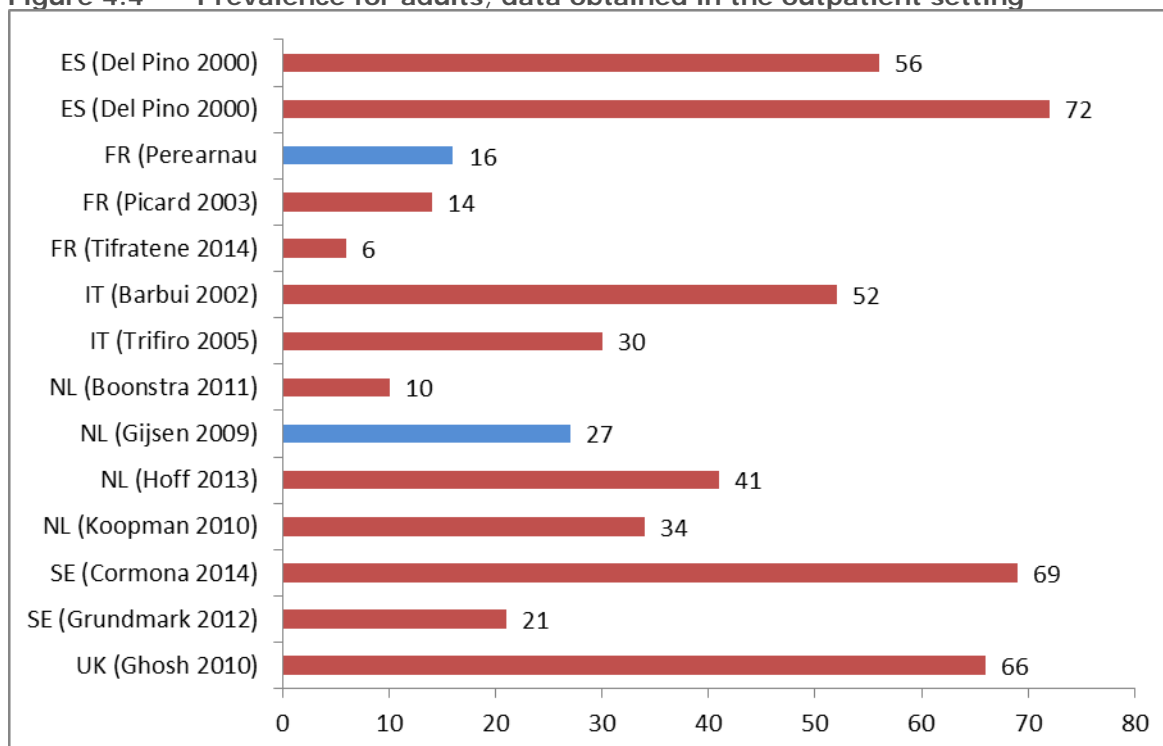
All numbers are based on questionnaires. In some studies, the questionnaires concern a specific medicinal product (group) and in others a general question on off-label use was posed. For a detailed overview of all studies and prevalence figures, reference is made to Annex G.

4.2.2 Prevalence in adults

The second part of the analysis of the systematic literature review (see section 2.3. for a description) focused on adults. Although almost all medicines are registered for use in adults, off-label use also occurs among the adult population. Off-label use may be due to the fact that medicines are usually registered for a limited number of indications, or not fully studied in specific patient groups such as pregnant women, the (eldest) elderly or people with specific comorbidities, e.g. renal and hepatic failure. The literature review (23 studies including data from six EU Member States) showed that off-label use in adults frequently occurs in the hospital setting: a range in prevalence of 7% to 95% of all prescriptions was found (Figure 4.3). The study where 95% of the prescriptions were off-label was a small-scale study into prescription of the antibiotic Daptomycin. Other studies with a high prevalence of off-label use covered a range of therapeutic areas (oncology, autoimmune diseases, and palliative care) and use during pregnancy. Data obtained outside the hospital (13 studies including data from 6 EU Member States) showed a prevalence range of 6-72% of all prescriptions to be off-label (Figure 4.4). Again, high prevalence of off-label use was found in a variety of therapeutic areas (cardiology, neurology, psychiatry, and asthma/COPD). Finally, table 4.2 shows that a majority of a diverse group of prescribers states to prescribe off-label. Exact details as well as the exact literature references can be found in Appendix F.

**Figure 4.3** Prevalence for adults; data obtained in the hospital setting

The figures in the red bars are expressed as percentage of all adult patients included in the study at issue. All other figures are expressed as percentage of the total number of prescriptions investigated in that particular study. Some studies did not provide an overall off-label figure, but prevalence figures per disease area / indication or per ATC-class / drug substance. In that case, we reported the highest figure. For a detailed overview of all studies and prevalence figures, reference is made to Annex F.


Figure 4.4 Prevalence for adults; data obtained in the outpatient setting


Blue bars are expressed as percentage of the total number of prescriptions investigated in that particular study. All other figures are expressed as percentage of all adult patients included in the study at issue. Some studies did not provide an overall off-label figure, but prevalence figures per disease area / indication or per ATC-class / drug substance. In that case, we reported the highest figure. The data outside the hospital were in most cases (>85% of all studies included) retrieved from prescription databases or (electronic) medical records. For a detailed overview of all studies and prevalence figures, reference is made to Annex F.

Table 4.2 Prevalence of off-label prescribing by HCPs in adults

Member State	Percentage of physicians	Specialist / specialism
DE (Ditsch 2011)	91	Obstetrics and gynaecology
DE (Steinhoff 2012)	81	Neurology
FR (Rolland 2014)	75	Alcohol abuse specialists
NL (Jochemsens 2009)	100*	General practitioners
UK (Hodgson 2000)	65	Psychiatrists
UK (Haw 2007)	94	Hospital psychiatrists

*Refers to children and adults.

All numbers are based on questionnaires. In some studies, the questionnaires concern a specific medicinal product (group) and in others a general question on off-label use was posed. For a detailed overview of all studies and prevalence figures, reference is made to Annex G.

4.3 Areas of specific interest

In this section, areas of specific interest regarding off-label use are described. These areas were obtained from the literature study (see section 2.3) and the stakeholder interviews (see section 2.4). The results of the literature study are shown in Annexes E, F and G.



Off-label use in children is still widespread as was shown in the literature review described in the last section and was confirmed by many different types of stakeholders (source: interviewees regulatory: Austria, Belgium, Denmark, France, Finland, Ireland, Italy, the Netherlands, Spain, Sweden, UK, EMA; interviewees reimbursement: the Netherlands; interviewees independent experts: Bulgaria, Czech Republic, Estonia, Malta; interviewees patient organisation: EAASM, EURORDIS, Irish Premature Babies; interviewees professional organisation: EAHP; interviewees industry: EFPIA, EUCOPE). Typical therapeutic areas of off-label use in children, derived from the literature study, include infectious diseases, cardiology, dermatology, pain treatment, alimentary tract and metabolism, the respiratory system and the central nervous system. Although studies on the extent of off-label use in the paediatric population differ in scope and patient population there does not seem to be a decrease in off-label prescribing after the introduction of the Paediatric Regulation.

Most studies reported in literature on off-label use in adults focus on specific therapeutic areas, such as oncology, psychiatry, or on expensive medicinal products, such as intravenous human immunoglobulins and TNF-antagonists (e.g. used in rheumatology). These areas were confirmed by the interviewed stakeholders as therapeutic areas where off-label use happens (see Table 4.3 for more specific information). The most frequently mentioned therapeutic area was oncology, including haematology. Areas identified also included rheumatology, macular degeneration, and neurology.

Rare diseases are defined in the EU as diseases with a prevalence of not more than five in ten thousand persons. During the interviews, several representatives stated to have no specific information on the extent of off-label use in rare diseases (source: interviewees regulatory: Denmark, Finland, Italy, Slovenia, UK; interviewees reimbursement: Slovenia; interviewees independent expert: Estonia, Greece). Other representatives stated that off-label use happens (although they could not specify to what extent exactly) as for many rare diseases there is no approved medicine, leaving off-label use as the only treatment option (source: interviewees regulatory: Austria, Belgium, France, the Netherlands, Portugal, Spain; interviewees reimbursement: Lithuania, the Netherlands; interviewees independent expert: Malta; interviewees patient organisation: EAASM, EURORDIS, IAPO, Irish Premature Babies; interviewees professional organisation: EAHP, EHA; interviewees industry: EFPIA, EUCOPE). A 2012 survey in France among rare disease centres (92 out of 131 centres participated) identified 480 off-label practises corresponding to 82 rare diseases. In a recent survey (source: oral communication by Eurordis patient organisation representatives; survey in progress), EURORDIS estimated that 23% of the participating patients with rare diseases benefit from an off-label use product (120 out of 524 responses). In Hungary, 2% of the authorized off-label cases concerns rare diseases (source: interviewee regulatory: Hungary).



Table 4.3 Therapeutic areas where off-label prescribing occurs according to representatives in the interviews

Field	Type of stakeholder who mentioned this area	Countries / European organisation where stakeholders come from
Oncology, including haematology	Regulatory	Belgium, Denmark, Finland, France, Hungary, Italy, Netherlands, Slovenia, Sweden, UK, EMA
	Reimbursement	Hungary, Lithuania, Netherlands, Slovenia
	Independent expert	Czech Republic, Greece, Malta
	Patient organisation	EAASM
	Professional organisation	EAHP
Rheumatology	Industry	EFPIA, EUCOP
	Regulatory	Netherlands, Slovenia
	Reimbursement	Hungary, Netherlands, Slovenia
	Independent expert	Malta
Psychiatry	Professional organisation	EAHP
	Regulatory	Hungary, Lithuania, UK
Macular degeneration	Reimbursement	Netherlands
	Regulatory	Ireland, EAHP, EUCOPE,
	Professional organisation	EAHP
Neurology	Industry	EUCOPE
	Regulatory	Italy
	Independent expert	Czech Republic, Greece
Clinical immunology	Professional organisation	UEMS
	Regulatory	Hungary
Dermatology	Independent expert	Greece
	Regulatory	Hungary, Netherlands
Ophthalmology	Reimbursement	Netherlands
	Regulatory	Hungary
Psychiatry combined with older age/dementia	Industry	EFPIA
	Independent expert	Estonia, Malta
Cardiovascular diseases	Regulatory	Italy
Gastrointestinal diseases	Regulatory	Italy
Immunology	Independent expert	Malta
Infectious diseases for children	Independent expert	Czech Republic
Infectious diseases general and respiratory diseases	Regulatory	Italy
Infertility	Professional organisation	UEMS
Urinary tract diseases	Regulatory	Italy

A number of representatives stated to have no specific information on off-label use in the elderly or not to know to what extent it might happen (source: interviewees regulatory: Denmark, Finland, France, Italy; interviewees independent expert: Greece, Malta). Some representatives think there is not much off-label use in the elderly (source: interviewees regulatory: Hungary, Sweden, UK; interviewees reimbursement: Lithuania; interviewees independent expert: Czech Republic; interviewees patient organisation: EURORDIS) and think it is lower than in children and in rare diseases (source: interviewee industry: from EUCOPE). Others think there is a considerable amount of off-label use in the elderly although there are not many data available (source: interviewees regulatory: Austria, Belgium, Portugal, Spain; interviewees independent expert: Estonia; interviewees professional organisation: EAHP). Literature data showed the following prevalence of off-label use in diseases that are more prevalent in the elderly: 6% (use of Alzheimer's disease medication in mild cognitive impairment), 17% (in cardiovascular disease as well as in asthma and COPD) and 56% (use of antipsychotics in behavioural and psychological symptoms of dementia). The Avastin®-Lucentis® case is also relevant for the elderly, but here off-label use is primarily evoked by the (costs of the) medicinal product and not by age itself.



For off-label use in pregnant women a number of representatives stated not to have specific information on whether or to what extent it might happen (source: interviewees regulatory: Austria, Belgium, Denmark, Italy, Spain; interviewees independent expert: Greece; interviewees industry: EUCOPE). Some representatives perceived the problem to be minor (source: interviewees regulatory: Finland, Hungary, Portugal, Sweden; interviewees reimbursement: Lithuania; interviewees professional organisation: EAHP) or related to some specific medicines or severe conditions (source: interviewees from Bulgaria, Hungary, Malta, Portugal, Slovenia; professional organisation: UEMS). Other representatives stated that off-label use in pregnant women happens or needs special attention (source: interviewees regulatory: France, the Netherlands, UK, Sweden; interviewees reimbursement: the Netherlands; interviewees independent expert: Czech Republic, Estonia; interviewees professional organisation: UEMS; interviewees industry: EFPIA) as many medicines are not approved for use in pregnant women, have contra-indications or lack information on the safe use in pregnancy. In Hungary, approximately 3% of the authorised off-label cases are for pregnant women, mainly for the prevention of habitual abortion (source: interviewees regulatory: Hungary). Some representatives referred to misoprostol being used to induce labour in pregnant women (source: interviewees independent expert: Bulgaria; interviewees patient organisation: EAASM, Irish Premature Babies; interviewees industry: EFPIA). The representative of *Irish Premature Babies* (interviewee patient organisation) expressed her concern with regard to the off-label use of misoprostol as, according to her, it has led to unnecessary harm to mothers to be and their infants. A French study showed that half of the 20 most prescribed medicines during pregnancy are off-label⁹ and French authorities pay particular attention to off-label use of medicines with teratogenic effects. The *Maltese* representative (interviewee independent expert) stated prescribers are very most aware in this area and limit prescribing to medicines for which experience of use in pregnancy is available.

Views on specific area per type of stakeholder

From the opinions described above it can be concluded that pharmacotherapy in children is widely seen an area of interest when it comes to off-label use by all types of stakeholders. The same holds for orphan diseases. For the elderly and pregnant women, the opinions are more divergent among stakeholders. However, there is not a clear pattern to be seen among different types of stakeholders in how they view off-label use in these areas. The fact that less information on the extent of off-label use in these two groups is available may be a reason for the diverse opinions. According to literature, clinical areas of interest regarding off-label use are oncology/haematology, psychiatry and rheumatology. These all represent unmet medical needs. These clinical areas were also mentioned by all types stakeholder groups, especially oncology (all types of stakeholder) and rheumatology (all types of stakeholders).



4.4 Drivers of off-label use

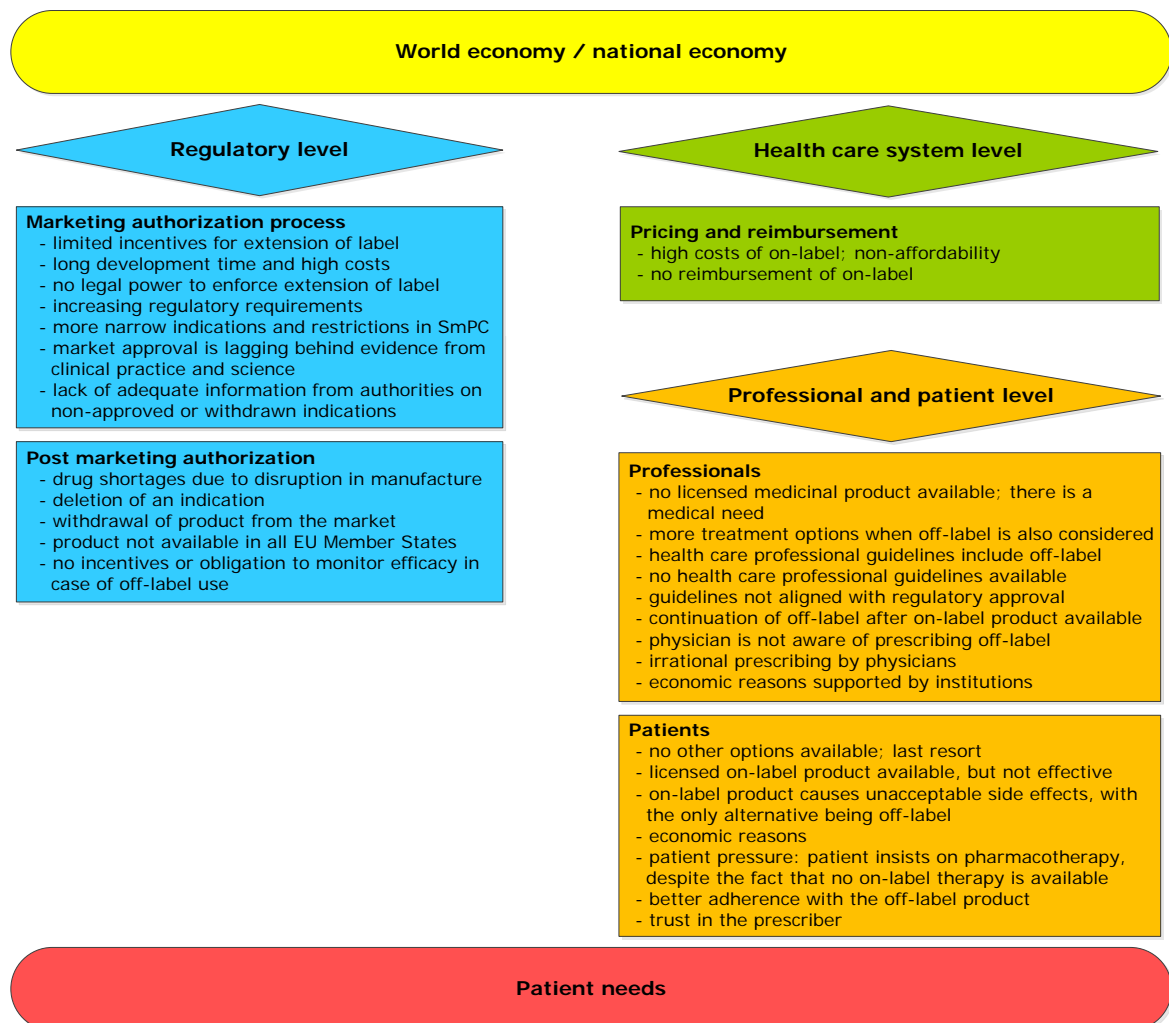
Key findings on drivers of off-label use

- Various drivers provoke off-label use of medicinal products. These drivers relate to the marketing authorisation process, post marketing authorisation events (e.g. disruption in manufacturing, withdrawal from the market), pricing and reimbursement, aspects connected with the work of healthcare professionals, and patient related factors.
- In specific cases, it is not a single driver, but rather a combination of drivers that provoke off-label use. Drivers may also change during the life cycle of a medicinal product that is used off-label.
- The nature of the drivers is sometimes complex and drivers may interact with each other. The relative contribution of, and interaction between, drivers is unknown.

As indicated in chapter 3 of this report, EU legislation strictly regulates the market authorisation of medicinal products with the aim of safeguarding public health of all EU citizens and protecting free movement of goods, but holds the individual Member States responsible for organizing their healthcare system, including pricing and reimbursement of medicinal products. Drivers can be related to the EU regulatory system as well as the national healthcare systems. Economics influences decisions of pharmaceutical companies to develop products and therefore influences, via the marketing authorisation system, the availability of medicinal products. Economics also influences the healthcare system (e.g. reimbursement) and herewith (indirectly) off-label use. These elements (economics, marketing authorisation system, healthcare system, patient needs) were used for depiction of the drivers in Figure 4.5 (see below). The drivers discussed in the following sections have been obtained from the literature search (see section 2.3) and the interviews with stakeholders (see section 2.4). The results of the literature study are shown in Annexes E, F and G.



Figure 4.5 Overview of drivers for off-label use; from literature and interviews



4.4.1 Regulatory and healthcare system level

4.4.1.1 Regulatory level

Marketing authorisation process

- There are limited incentives for pharmaceutical industry to extend the labelling of existing medicinal products; legislation allows for a one year extra market protection if a new indication is registered in the first eight years after a marketing authorisation has been granted and if this new indication brings significant clinical benefit over existing therapies; however, off-label sales will continue without investment in such a new indication anyway; and specifically for off-patent products, generic competition and/or low medicinal product price have a negative impact on return for investments in new indications (*source: literature; interviewees patient organisations: EAASM; interviewees professional organisations: UEMS; interviewees industry: EFPIA*).¹⁰⁻¹⁸
- Regulators/National Competent Authorities have no legal power to enforce marketing authorisation holders to include indications in the SmPC, even not when adequate (scientific) evidence is available. The same is true for other off-label



aspects, such as dosing advice, use in specific groups (with the exception for children, for which the paediatric regulation enforces the inclusion of all available evidence), contra-indications, and administration route; according to Sweden, it should be clarified which responsibility the MAH has to initiate changes and updates, other than formal applications for variations due to pharmacovigilance issues (*source: literature; interviewees regulatory: Sweden, Germany*).^{15 19 20}

- The requirements for marketing authorisation, as described in legislation and guidelines, have increased over the years. It may also take a long development time and high costs to investigate a new indication; preparing a dossier for a marketing authorisation extension and introduce the approved changes in production practice, takes a considerable effort; moreover, the pre-clinical studies performed for the original/first indication(s) might not be suitable for a new indication (*source: literature; interviewees regulatory: Belgium, Hungary, Ireland, Netherlands; interviewees reimbursement: Netherlands; interviewees patient organisations: Irish premature babies, EURORDIS*).²¹
- The SmPC only reflects patient categories which were included in the clinical trials for marketing authorisation, while neglecting other populations that may benefit from the medicinal product. MAHs make their development decisions – which are also considerable investments – on the basis of commercial arguments. Moreover, indications and contraindications are nowadays narrower than formerly (*source: literature; interviewees regulatory: Germany, France*).²²
- Science and clinical practice are much faster than the regulatory approval processes and as such market approval is lagging behind evidence; the information in the SmPC does not reflect all available evidence: results of clinical trials reported in scientific literature and efficacy/safety information gathered in daily medical practice are not always (immediately) included (*source: literature; interviewees regulatory: Germany*).^{20 21 23-26}

Post marketing authorisation events

- Disruption in the manufacturing of a product, leading to drug shortages and necessity to use other products off-label (*source interviewees regulatory: Sweden*).
- Despite marketing authorisation, a product may not be available in all EU Member States due to economic reasons, especially for lower income countries and countries with a small market (*source: interviewees regulatory: Denmark, Ireland, Portugal, Slovenia, Sweden; interviewees reimbursement: Lithuania, Slovenia; interviewees independent expert: Bulgaria, Czech Republic, Greece, Malta; interviewees patient organisations: EURORDIS; interviewees professional organisations: UEMS; interviewees industry: EUCOPE*).
- Products may be withdrawn from the market or a specific indication is deleted; in case of deletion of an indication the product may still be used off-label for that particular indication if the deletion was not for reasons of safety (*source: literature*).²⁷
- There is no obligation to monitor and report on the efficacy in case of off-label use (only on adverse drug reactions), neither for marketing authorisation holders nor for healthcare professionals; absence of gathering real world data hampers extension of (scientific) evidence (*source: interviewees regulatory: Spain, Germany; interviewees patient organisations: IAPRO*).²⁸
- Competent authorities can require MAHs to perform post-authorisation studies, yet not for off-label indications (*source: literature, JL/ author*).²⁹

4.4.1.2 Healthcare system level

Pricing and reimbursement:

- At the health care system level pricing may be a reason for off-label prescribing in case the 'on-label product' is more expensive than the 'off-label product' and the cheaper off-label product is (also) reimbursed; this may also be the reason that



occasionally generics are prescribed for an indication for which the original product is not yet out of patent (*interviewees regulatory: Denmark, France, Spain; interviewees patient organisations: EAASM, IAPO; interviewees professional organisations: EAHP, EHA; interviewees industry: EFPIA, EUCOPE*).

- Pricing may even lead to non-affordability in some EU Member States; medicinal products are sometimes not (fully) reimbursed, which may lead to non-affordability for patients (*Source: interviewees regulatory/reimbursement: Slovenia; interviewees independent expert: Malta*).
- Some interviewees refer to the fact that sometimes off-label use of a medicinal product is reimbursed while use of the 'on-label product' is not, leading to off-label use despite the presence of an on-label product (*interviewees regulatory: Finland; interviewees independent expert: Estonia; interviewees industry: EUCOPE*).

4.4.1.3 Drivers per stakeholder

In this section, the drivers as mentioned in the previous sub-sections are grouped according to type of stakeholder. This is done in order to be able to distinguish between the views of different types of stakeholders. Only the most frequently mentioned drivers are summarized.

Regulatory and reimbursement stakeholders

Representatives within this group of stakeholders frequently mention that the requirements for marketing authorisation, as described in legislation and guidelines, have increased over the years (*Belgium, Hungary, Ireland, Netherlands*). Also, the fact that, despite marketing authorisation, a product may not be available in all EU Member States due to economic reasons is frequently mentioned by interviewees in this stakeholder group, especially by representatives who live in countries with a small market (*Denmark, Ireland, Lithuania, Portugal, Slovenia, Sweden*). Some interviewees mention the fact that pricing may be a reason for off-label prescribing in case the 'on-label product' is more expensive than the 'off-label product' and the cheaper off-label product is (also) reimbursed (*Denmark, France, Spain*).

Independent experts

The driver that dominates within this group of stakeholders frequently is the fact that, despite marketing authorisation, a product may not be available in all EU Member States due to economic reasons. These experts live in countries with a small market (*Bulgaria, Czech Republic, Greece, Malta*).

Patient organisations

Patient organisations mentioned a variety of factors that might drive off-label use, but they do not have a driver that clearly stands out. Two organisations (*Irish premature babies, EURORDIS*) mention the increased requirements for marketing authorisation. Two other organisations (*EAASM, IAPO*) mention the fact that pricing may be a reason for off-label prescribing in case the 'on-label product' is more expensive than the 'off-label product' and the cheaper off-label product is (also) reimbursed.

Professional organisations

Like patient organisations, the professional organisations mentioned a variety of factors that might drive off-label use, but without a driver that clearly stands out. Two organisations (*EAHP, EHA*) mention the fact that pricing may be a reason for off-label prescribing in case the 'on-label product' is more expensive than the 'off-label product' and the cheaper off-label product is (also) reimbursed. Other drivers were only mentioned by one organisation.



Industry

Both interviewed organisations (*EFPIA*, *EUCOPE*) mention the fact that pricing may be a reason for off-label prescribing in case the 'on-label product' is more expensive than the 'off-label product' and the cheaper off-label product is (also) reimbursed. *EFPIA* mentioned the limited incentives for the industry to extend the labelling of existing medicinal products, whereas *EUCOPE* refers to the fact that a product may not be available in all EU Member States due to economic reasons.^{III}

4.4.2 Professional and patient level

4.4.2.1 Professional level

Professionals:

- In the absence of an appropriate authorised drug, there is no other choice than prescribing off-label. This is especially the case for rare diseases, rare medical situations, (severe) diseases or medical situations that are difficult to treat, and in specific patient groups, such as children and pregnant women. Off-label use thus increases the opportunities to treat (specific) patients; sometimes off-label use is last resort (source: literature; interviewees regulatory: Belgium; Denmark, Finland, Ireland, Portugal, Sweden, Spain; interviewees independent expert: Czech Republic, Bulgaria, Estonia; interviewees professional organisations: EAHP; interviewees industry: *EUCOPE*).³⁰⁻³²
- Off-label use of a medicinal product is part of a healthcare professional treatment guideline or hospital/institution formulary (source: literature; interviewees from interviewees regulatory Netherlands, Denmark, Finland; interviewees reimbursement: Netherlands; interviewees professional organisations: *UEMS*).^{30 33 34}
- Healthcare professional guidelines are not aligned with regulatory approval; sometimes an indication is not approved by medicinal product authorities, but recommended as first choice in healthcare professional guidelines, because for individual patients the benefit-risk balance may be judged as positive by health care professionals (e.g. methylphenidate used in adults with ADHD in the Netherlands) (source: literature).¹³
- Off-label prescribing provides more options for the prescriber to give a better treatment for patients; new research results may be implemented directly even while they are not yet part of a guideline (source: interviewees regulatory: Denmark, Hungary, Finland, Spain; interviewees independent expert: Estonia, Czech Republic; interviewees patient organisations: Irish Premature Babies, EURORDIS; interviewees professional organisations: EHA; interviewees industry: *EFPIA*).
- Absence of healthcare professional guidelines; if no clear guidance is given on the on-label options, off-label use may occur (source: literature; interviewees professional organisations: *UEMS*).³⁵
- Continuation of off-label use after an on-label medicinal product has become available; this may be due to favourable practical experience with the off-label product, unwillingness of patients to switch, or unawareness of the on-label alternative (source: literature).³⁶
- Economic reasons were also mentioned; for example, the medical advisory board of a teaching or secondary hospital may decide to support off-label use for economic reasons (for example that they are aware that if they prescribe the cheaper option, they can provide the treatment to more patients)(interviewees regulatory: Belgium, Denmark; interviewees patient organisations: EAASM, Irish Premature Babies; interviewees industry: *EFPIA*, *EUCOPE*).

^{III} It also depends on the size of the stakeholder group whether an argument is considered as a main argument as in some stakeholder groups less interviews have been performed.



- Physicians are not aware of the fact that a drug is prescribed by them off-label; during the (electronic) prescription process no signal is given on this. (source: literature; interviewees regulatory: Germany, Netherlands, Austria; interviewees reimbursement: Netherlands)^{28 37 18 27 38 39}
- Irrational prescribing practice; for example, false beliefs of physicians that a lower dose will lead to less side effects or personal conviction of higher efficacy compared to other (on label) medicines; or literature data suggest that the medicinal product could be of value in an off-label manner; for example, based on mechanism of action of the active substance (source: literature).³⁹⁻⁴⁸

4.4.2.2 Patient level

- There are no other options available for a particular patient; off-label may be last resort; (source: literature; interviewees regulatory: Belgium, Finland, France, Hungary, Netherlands, Portugal, Sweden, UK; interviewees reimbursement: Netherlands; interviewees independent expert: Bulgaria, Greece, Malta; interviewees industry: EFPIA, EUCOPE).³⁰⁻³²
- An (authorised) 'on-label product' is available, but appears not to be effective or causes unacceptable side effects in an individual patient; leading to the use of other medicines that are off-label (source: literature; interviewees regulatory: UK; interviewees professional organisations: EAHP).^{49 50}
- Patient pressure; patients may insist on pharmacotherapy, even when this is off-label and not evidence based. Patients seek the most effective treatment, sometimes based on information they find on the internet or on information they exchange with other patients or by participating in patient organisations; self-diagnosing/prescribing and different types of access to prescription drugs over the internet (also outside EU) are of concern; (source: literature; interviewees regulatory: Austria, Hungary, Spain, Sweden; interviewees independent expert: Malta; interviewees patient organisations: EURORDIS, Irish Premature Babies; interviewees professional organisations: EHA).^{42 51}
- Economic reasons can also drive off-label use at a patient level, especially in lower income countries and when patients have to pay a medicinal product (partly) out-of-their own pocket. In *Bulgaria* and the *Czech Republic*, for example, the level of income is low, while the prices of medicines are as high as in a country like *Germany*. (source: interviewees independent expert: Bulgaria, Czech Republic)
- Other factors mentioned include better adherence to the medication (for example when there is a product that the patient can use in tablets adherence may be better than for an injection), trust in the prescription (source: interviewees regulatory: Portugal; interviewees independent expert: Czech Republic,) and off-label self-medication by the patient (Source professional organisations: UEMS).

4.4.2.3 Drivers per stakeholder

In this section, the drivers as mentioned in the previous sub-sections are grouped according to type of stakeholder. This is done in order to be able to distinguish between the views of different types of stakeholders. Only the most frequently mentioned drivers are summarized.^{mmm}

Regulatory and reimbursement stakeholders

A number of representatives within this group of stakeholders mention the absence of an appropriate authorised drug as a driver: there is no other choice than prescribing off-label. Off-label use thus increases the opportunities to treat (specific) patients; sometimes off-label use is last resort for a particular patient (*Belgium; Denmark, Finland, France, Hungary, Ireland, Netherlands, Portugal, Sweden, Spain, UK*). The fact that off-label

^{mmm} It also depends on the size of the stakeholder group whether an argument is considered as a main argument as in some stakeholder groups less interviews have been performed.



prescribing provides more options for the prescriber to give a better treatment for patients is also mentioned by some of the stakeholders in this group (*Denmark, Hungary, Finland, Spain*). Another driver mentioned by some interviewees in this stakeholder group is when off-label use of a medicinal product is part of a healthcare professional guideline or hospital/institution formulary (*Netherlands, Denmark, Finland*). Unawareness among physicians about the fact that a drug is prescribed by them off-label is another driver mentioned by this group of stakeholders. (*Germany, Netherlands, Austria*). Finally, patient pressure to get a medicine while it is off-label is a driver that is recognized within this group of stakeholders.

Independent experts

Also within this group the absence of an appropriate authorised drug is seen as an important driver for off-label use as it increases the opportunities to treat (specific) patients; sometimes off-label use is last resort for a particular patient (*Czech Republic, Bulgaria, Estonia, Greece, Malta*). According to two experts from small markets (*Bulgaria, Czech Republic*) economic reasons can drive off-label use in lower income countries in case patients have to pay a medicinal product (partly) out-of-their own pocket.

Patient organisations

Some of the interviewees in this group of stakeholders consider the fact that off-label prescribing provides more options for the prescriber to give a better treatment for patients as a driver (*Irish Premature Babies, EURORDIS*). Moreover, economic reasons (for example awareness among hospital boards or doctors that if they prescribe the cheaper option, they can provide the treatment to more patients)(*EAASM, Irish Premature Babies*). Patient pressure is another driver mentioned in this group (*EURORDIS, Irish Premature Babies*).

Professional organisations

The professional organisations mentioned a variety of factors that might drive off-label use, but without a driver that clearly stands out. One representative within this group of stakeholders referred, for example, to the absence of an appropriate authorised drug is a driver (*EAHP*); someone else mentioned the fact that more treatment options are available (*EHA*) and yet another person referred to the fact that including off-label prescribing in a guideline might be a driver (*UEMS*).

Industry

EUCOPE referred to the absence of an appropriate authorised drug for a particular patient being a driver, while the *EFPIA* mentioned the fact that more treatment options are available. Economic reasons for off-label use were mentioned by both of them; for example, the medical advisory board of a teaching or secondary hospital may decide to support off-label use for economic reasons (*EFPIA, EUCOPE*).



4.4.3 Specific cases illustrating drivers

4.4.3.1 Avastin® and Lucentis®

Avastin® is a medicine containing bevacizumab as active substance. Bevacizumab is a humanised monoclonal antibody that binds selectively to the human vascular endothelial growth factor (VEGF) and hence blocks angiogenesis, a process that occurs in a variety of diseases, especially in cancer. Avastin® was registered in the EU in January of 2005 for first-line treatment of patients with metastatic carcinoma of the colon and rectum (used in combination with intravenous 5-fluorouracil-based chemotherapy).

Angiogenesis occurs also in some eye diseases such as age-related macular degeneration (AMD) and therefore bevacizumab and other angiogenesis inhibitors may also be effective in the treatment of AMD. Macugen® and Lucentis® both contain an angiogenesis inhibitor as active substance (Pegaptanib and Ranibizumab, respectively). Macugen® was registered in Europe in 2006 and Lucentis® in 2007, for the treatment of wet macular degeneration and AMD, respectively. Before the registration of Macugen® and Lucentis®, Avastin® had already been found to be effective in the treatment of macular degeneration and used in an off-label manner in AMD patients,^{52,53}. The driver for this was the lack of a licensed medicinal product for AMD.

When Macugen® was approved by the EMA in 2006, ophthalmologists observed poorer efficacy and disappointing results in some patients. This led to further experimentation with Avastin® and off-label use of this medicine in patients that did not respond well to either Macugen® or photodynamic therapy, the only available treatments at that time. The driver for off-label use of Avastin® changed at that point from unavailability of an alternative to better efficacy compared to the 'on-label' licensed product.

With the registration of Lucentis®, the driver changed again and became a matter of costs: Macugen® led to stabilisation of vision loss whereas Lucentis® not only prevented further loss of vision but also led to improvement in visual acuity; however, the price of Lucentis® was higher than that of Macugen®.

Reimbursement of the costs of Lucentis® has continuously been a reason for debate. Roche tried to prevent off-label use of Avastin® by warning about safety issues linked to its off-label useⁿⁿⁿ; a direct comparison of the effectiveness of Lucentis® and Avastin® was not undertaken. In the end, public research funds were used to prove that the two medicines were indeed similarly safe and effective for this indication. Based on the clinical evidence of Bevacizumab and Ranibizumab being equally effective and safe in the treatment of AMD, it is now well accepted by HCPs in The Netherlands that Avastin® is the medicine of first choice⁵⁴. In Italy, in 2014, the competition watchdog fined Novartis and Roche after concluding that the two companies had agreed to portray the cheaper Avastin® as more dangerous than Lucentis®. Similarly, a Spanish consumer group formally asked the country's antitrust watchdog to investigate claims that Roche and Novartis conspired to keep patients

ⁿⁿⁿ Health Canada Endorsed Important Safety Information on Avastin (bevacizumab). Retrieved on March 2016 from <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2008/14494a-eng.php>.



from using a cheaper macular degeneration drug in favour of their more expensive Lucentis® product^{ooo}. France and the EU also launched separate investigations to find out whether Roche and Novartis indeed colluded to protect sales of Lucentis®. In June 2014, the Italian medicines agency decided to reimburse Avastin® for AMD^{ppp}. In 2014, France made its move to exclude Lucentis® of drug coverage and replace it with Avastin®. Novartis, Roche, and the European Federation of Pharmaceutical Industries and Associations (EFPIA) were arguing that off-label prescribing decisions should be based on medical need rather than economic pressure^{qqq}. In June 2015, the French ANSM (Agence Nationale de Sécurité du Médicament) published a recommendation for temporary use (RTU) for Avastin® for the treatment of AMD^{rrr}. The Avastin® RTU became effective as of September 1st, 2015 and is valid for a period of 3 years. In its 29th June 2016 decision, the Conseil d'Etat dismissed the applications brought by Les Entreprises du Médicament (LEEM), Roche SAS, Novartis Europharm limited and Novartis Pharma, seeking to revoke the provisions of decree n° 2014-1703 of 30th December 2014 amending rules relating to the preparation of Temporary Use Recommendations (RTU) prepared pursuant to I of article L. 5121-12-1 of the Public Health Code. In its 24th February 2017 decision, the Conseil d'Etat dismissed the applications brought by Roche and Novartis seeking to revoke the 24th of June 2014 decision of the National Agency for Medicines and Health Products safety recommendation to treat patients with neovascular age-related macular degeneration. Thus, France maintains its recommendation for Avastin®^{sss}.

4.4.3.2 Methylphenidate

Concerta® is a medicine containing Methylphenidate as active compound. Methylphenidate is a stimulant drug that can improve mood and attention and is hence prescribed for Attention Deficit Hyperactivity Disorder (ADHD). An Internet search performed on March 2016 shows that, apart from Concerta®, there are also other medicines available containing Methylphenidate, at least in Finland, Germany, Ireland, Spain, The Netherlands and the United Kingdom^{ttt}. Some of these medicines are only registered for use in children with ADHD while others (Concerta®, Medikinet CR®, and some generics) are also approved for use in adults (but only as continuation therapy, i.e. therapy started already in childhood and is still successful).

The off-label use of Concerta® in adults has generated quite some debate in the last years. The registration of Concerta® for adults was rejected by competent authorities in 2010 due to doubtful quality of the research performed with this drug and to high frequency of side effects. This rejection contrasted with the opinion of several psychiatrists and ADHD experts, who continued to defend the value of Concerta® as the most effective drug available for adults with ADHD. They went on with their intention to include Concerta® in the professional guidelines for ADHD treatment as the drug of first choice for treatment of adults with ADHD. Indeed, the Dutch

^{ooo} Spanish consumers ask watchdog to probe Roche, Novartis. Retrieved on March 2016 from <http://www.law360.com/articles/531457/spanish-consumers-ask-watchdog-to-probe-roche-novartis>

^{ppp} Italy to Fund Unapproved Use of Roche Drug to Cut Costs. Retrieved on March 2016 from <http://www.bloomberg.com/news/articles/2014-06-10/italy-to-fund-unapproved-use-of-roche-drug-to-cut-costs>

^{qqq} Roche, Novartis protest moves in EU to pay for off-label Avastin. Retrieved on March 2016 from <http://www.fiercepharma.com/story/roche-novartis-protest-moves-eu-pay-label-avastin/2014-07-28>

^{rrr} L'ANSM établit la RTU d'Avastin® (bevacizumab) dans la dégénérescence maculaire liée à l'âge (DMLA) dans sa forme néovasculaire - Point d'information. Retrieved on February 2017 from

<http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/L-ANSM-etablit-la-RTU-d-Avastin-R-bevacizumab-dans-la-degenerescence-maculaire-liee-a-l-age-DMLA-dans-sa-forme-neovasculaire-Point-d-information>

^{sss} AVASTIN® 25 mg/ml, solution à diluer pour perfusion. Retrieved on February 2017 from <http://ansm.sante.fr/Activites/Recommandations-Temporaires-d-Utilisation-RTU/Liste-des-specialites-faisant-actuellement-l-objet-d-une-RTU/Liste-des-specialites-faisant-l-objet-d-une-RTU-AVASTIN-R-25-mg-ml-solution-a-diluer-pour-perfusion>

^{ttt} <http://mri.cts-mrp.eu/Human/> Heads of Medicines Agencies, Human MRIndex. Consulted on March 2016.



professional guideline recommends Methylphenidate as the first-choice drug for ADHD treatment in adults, because for individual patients the benefit-risk balance may be judged as positive by HCPs. The driver for off-label in this case is the inclusion of off-label use in a treatment guideline.

4.4.3.3 Misoprostol

Misoprostol (Cytotec®) was developed in the early 70s for prophylaxis and therapy of gastroduodenal ulcers. It has been available on prescription in 100-µg and 200-µg tablets at the international market since 1986. The SmPC states pregnancy as contraindication, given that it may provoke uterine contractions. However, exactly because of this side effect, Cytotec® has been used off-label for many years in the areas of gynaecology and obstetrics to weaken the uterus and induce contractions. Such effects may be sought for to achieve cervical ripening before uterine instrumentation, induction of labour at term in viable pregnancies, treatment of missed and incomplete miscarriages (as alternative to curettage) or induction of abortion, or for therapy for post-partum haemorrhage.

Originally, the drivers for the off-label use of Cytotec® were probably the lack of a comparable registered alternative combined with the low price of this medicine. Little incentive existed for the pharmaceutical company to add an indication to the label of misoprostol. First, because clinicians were already using it for obstetrics and, second, to avoid potentially damaging discussions about the drug's use for inducing abortion⁵⁵. Despite scientific evidence to support its use, the marketing authorisation holder did not seek approval for new indications.

In France, the National Agency for the Safety of Medicines and medicinal products (ANSM, Agence Nationale de Sécurité du Médicament et des produits de santé) cautioned about the off-label use of Cytotec® for the induction of labour because of the risk of serious side effects such as uterine rupture, bleeding, or abnormal foetal heart rate. Misodel, approved for the induction of labour, could provide an on-label option. However, the High Authority for Health (HAS, Haute Autorité de Santé) did not recommend the inclusion of Misodel on the list of reimbursable products for hospital use due to insufficient proof of clinical benefit when compared to the intravaginal administration of prostaglandin E2^{uuu}. Recently (i.e. from 2012), pharmaceutical companies obtained marketing authorisations of products with misoprostol in several EU countries for indications in the areas of gynaecology and obstetrics^{vvv}. And the CHMP gave a positive scientific opinion on Hemoprostol in 2014, within the scope of the EMA's cooperation with the World Health Organisation. Hemoprostol is indicated in women of childbearing age for treatment of post partum haemorrhage due to uterine atony in situations where intravenous oxytocin is not available.

^{uuu} <http://sages-femmes.neufmois.fr/news/misodel-pas-prise-en-charge-en-raison-dun-beneficeriesques-concluant>.
Consulted on March 2016.

^{vvv} <http://mri.cts-mrp.eu/Human/> Heads of Medicines Agencies, Human MRIndex. Consulted on March 2016



4.5 National frameworks

Key findings on practices of off-label use at Member State level

- Ten out of the 21 countries that participated in the study have specific policy tools in place for off-label use. These policy tools vary in scope and intensity. Examples of policy tools incorporated by EU Member States are:
 - Legal frameworks to issue temporary recommendations for use and permission to prescribe off-label such as the “temporary recommendations for use (RTU) scheme” in France and the Hungarian system where prescribers or their organisations have to ask for permission to prescribe a product off-label.
 - Measures to regulate reimbursement, for example France and Italy explicitly allow for reimbursement of off-label use also when (on-label/authorized) alternatives exist.
 - Policy tools providing guidance for prescribers such as the General Medical Council Guidance (Good practice in prescribing and managing medicines and devices, 2013) in the UK.
 - Policy tools where professional standards are leading, such as The Netherlands where off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use.
 - Policy tools focused on the patient, for example regarding the necessity to give informed consent needed in many Member States or the fact that for serious interventions, upon request of the patient, a HCP has to register for what intervention the patient has given consent (The Netherlands).
- In EU Member States without specific policy tools on off-label use, the dominant view is that off-label use is an issue to be dealt with at the level of the prescriber rather than at the regulatory or healthcare system level. Prescribers are trusted to know what is best for the well-being of the patient, with the medical need of the patient leading their decisions. Yet, it is also mentioned that lack of clarity about the liability is an issue in case of off-label prescribing and that patients should be properly informed and provide consent.
- No concrete foreseen practices for off label use in EU-Member States were identified.

As pointed out before, Member States have their own rules in place with regard to the prescription of medicines, including off-label prescribing. This is not harmonized. In some countries special provisions about off-label use are included in the national law, while other countries have good practice guidelines/professional recommendations and other countries use reimbursement decisions.

This section describes the practices in 21 Member States. The information in this section is mainly derived from interviews with representatives from these Member States (see section 2.4.1) ^{www}. We distinguish two groups of Member States (Figure 4.7) to discuss the standing and foreseen practices^{xxx} (between brackets the background of the representative(s) of the country:

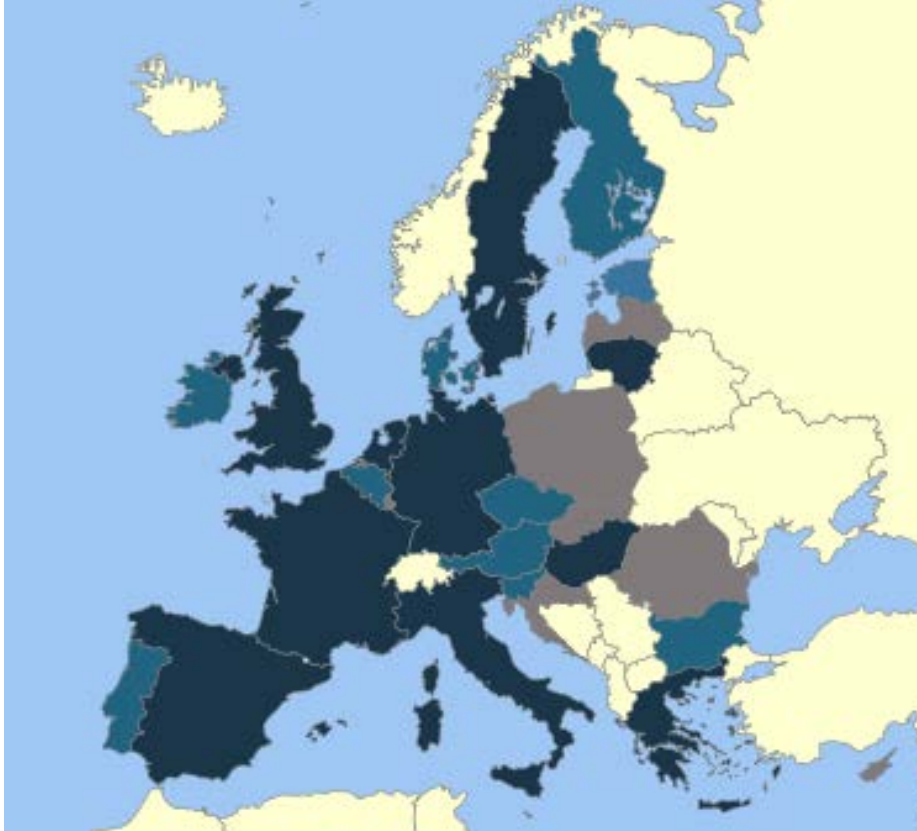
^{www} The information is supplemented by experts from the Commission Expert Group on Safe and Timely Access to Medicines for Patients (“STAMP”)

^{xxx} N=21 Member States; Member States that did not respond to our request for participation included: Croatia, Cyprus, Latvia, Luxembourg, Poland, Romania, and Slovakia.



1. Countries where no specific regulation with regard to off-label use is in place: Austria (Agency, regulatory), Belgium (Agency, regulatory), Bulgaria (independent expert, MD), Czech Republic (independent expert, MD), Denmark (Agency, regulatory and Ministry of Health), Estonia (independent expert, MD), Finland (Ministry of Health, regulatory), Ireland (Agency, regulator), Malta (independent expert), Portugal (Agency, regulatory), and Slovenia (Agency, regulatory and reimbursement) (n=11);
 2. Countries with specific legislation or related measures: France (Agency, regulatory), Germany (Agency, regulatory), Greece (independent expert, health politics & economics), Hungary (Ministry of Social Affairs and Health, regulatory; National Health Insurance Fund, reimbursement), Italy (Agency, regulatory), Lithuania (Ministry of Health, reimbursement), the Netherlands (Ministry of Health, regulatory and reimbursement), Spain (Agency, regulatory), Sweden (Agency, regulatory; Dental and Pharmaceutical Benefits Agency, regulatory) and the United Kingdom (Public Health England; Department of Health, Agency; regulatory) (n=10).
- The reason to separate between those two groups is that views on off-label use may differ and that foreseen practices may differ.

Figure 4.7 EU Member States and regulation of off-label use



Dark blue: countries with regulation; light blue: countries without regulation; grey: countries not participating

4.5.1 Member States without specific regulation or policy tools

Eleven countries included in this analysis reported not to have specific regulation or policy tools in place at the regulatory and/ or healthcare system level to regulate off-label use. Of course, these countries have regulation or policy tools in place to regulate the prescribing of medicines in general, which include off-label use. But, apart



from that there are no regulations or policy tools specifically focussing on off-label use. These countries include: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, Ireland, Malta, Portugal, and Slovenia. In this section, we first describe shortly the overall picture for these countries with regard to off-label practices: current practices, ways to identify off-label use and future plans. Annex H includes country-specific information.

Current practice: off-label prescribing is the responsibility of the prescriber

In countries without specific regulation or policy tools on off-label use, no specific mention of off-label use is made within the law and no specific reimbursement measures are taken.^{yyy} A main argument for not having specific measures in place is that off-label use is the responsibility of the prescriber; the prescriber is autonomous to prescribe. This latter responsibility is mentioned in the law in most countries, but not specifically for off-label use. The fact that off-label use is not included in the law is interpreted differently.

Despite different interpretations of not having included off-label use in the law, the dominant view in this group of countries is that off-label use is an issue that should be dealt with in the context of the prescriber-patient relationship rather than at the regulatory or healthcare system level. The idea behind this is that prescribers know what is best for the well-being of the patient and that the medical need of the patient is leading in their decisions. Yet, respondents from these countries see that the prescriber holds more responsibility in case of off-label prescribing and patients should be properly informed and provide consent. It is not known to what extent this occurs in clinical practice. No guidelines that explicitly include guidance on off-label use seem to be available.

Ways to identify off-label use

None of the Member States without specific off-label regulation or policy tools has systems in place to identify off-label use. Most of them refer to adverse events that should be reported in accordance with the EU Pharmacovigilance legislation, as it should be done for on-label use.

Future plans

Most Member States in this group do not consider new measures or policy tools. Half of them think their current measures are adequate. In some Member States, there is debate, especially in Belgium and Denmark. The Belgian Health Care Knowledge Centre (KCE) published a report as to how off-label use could be regulated (see also the section on Belgium in Annex H). Denmark, where the five regions have an important position in the healthcare system, debates as to whether the regions should have the authority to make guidelines and to decide on whether which medicines can be described.

4.5.2 Member States with regulation or policy tools

Ten countries included in this analysis have specific regulations or policy tools in place. These are: France, Germany, Greece, Hungary, Italy, Lithuania, the Netherlands, Spain, Sweden, and United Kingdom. Annex H includes country-specific information. In this section we describe the overall picture. The information is derived from the interviews/questionnaires of stakeholders in the country. As they differed in the

^{yyy} An exception is Austria where for very expensive medicines health insurers request information on the indication for which the medicine was prescribed.



amount of information that was provided, policy tools of some countries are described in more detail than others. Whenever possible and relevant, text provided by the stakeholders has been literally taken over.

Current practice: different approaches to regulate off-label use

The solutions with regard to off-label use nine Member States adopted differ in their approach and intensity. Moreover, the focus of the regulation is different. Table 4.4 shortly summarises policy tools in place in the different countries (for more detailed descriptions per country: see Annex H). These policy tools can be distinguished into different groups.

Legal frameworks to issue temporary recommendations for use or permission to prescribe off-label

France, Hungary, Italy, and Spain have legal measures in place to regulate requirements for off-label use.

France: Temporary recommendations for use (RTU)

(Information source: interviewees regulatory France and Emmerich et al 2012⁵⁶)

In France, physicians are free to prescribe medicines outside the scope of their marketing authorizations (MA) if they deem it necessary for their patients, given the scientific knowledge and the absence of available alternative treatment. However, in that situation, they must justify their choice and inform the patient of the status of the prescription, the risks and the benefits. Moreover, France has a “temporary recommendations for use (RTU)” scheme in place (n° 2011-2012 act enacted 29th December 2011). This act was established after the Mediator® health scandal which took place in France in 2011. Several think tanks, composed of members of Parliament and experts, were set up. These think tanks pointed out the lack of available information on off-label prescription practices and the lack of supervision of those prescriptions by the French Agency, ANSM.

The objectives of the RTU system are: 1) safer off-label use of medicines as patients should be monitored through a protocol, 2) to improve the knowledge regarding efficacy and safety of off label use, and 3) to encourage the pharmaceutical companies to file an MA extension. The first RTU has been enacted by ANSM in March 2014. Until 2016, 10 RTUs have been enacted (three in 2014 and seven in 2015).

A RTU is set up at the initiative of ANSM. Before a RTU can be issued several factors must be taken into consideration such as the quality of the scientific evidence, the drug safety, the prognosis associated with a given disease (the severity of the disease) and the frequency of the disease’s occurrence.⁵⁶ ANSM informs the marketing authorization holder (MAH) about the need of a RTU and asks him to provide all available data on the concerned indication. A RTU can be notified, in accordance with the European Court of Justice court cases to fulfil special needs, if the benefit/risk ratio of the medicinal product is presumed to be favourable, in situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product should be administered, for which there is no alternative medicinal product with the same active substance, the same dosage and the same form. The RTU notably specifies the indication and the posology of the medicine. It should be noted that for products that, in the absence of a RTU, prescribers are free to prescribe a medicine off-label in case an appropriate alternative authorised medicine is absent and the off-label use is expected to improve or stabilise the clinical condition of the patient. When a prescriber prescribes a medication as part of a RTU, this should be mentioned on the prescription, so that the pharmacist knows that the prescription is



within the RTU and is able to control the prescription within this context. The physician has to inform the patient of the off label use and of the potential benefits and risks attendant to the use. As such, RTU offers, for public health reasons, coaching and securing off-label practices. A medicine covered by a RTU can be reimbursed by the national health insurance. The Ministry of Health, the French National Authority of Health (HAS), the national health insurance, the National Cancer Institute, Centers of expertise for rare disease are invited to report to ANSM off label uses in case they believe that an RTU may be elaborated. Additionally, the National Health Insurance and ANSM have decided to work together sharing their information in order to identify off label practices

The RTU includes the obligation for the MAH to set up a follow up of patients based on safety and efficacy information, and real conditions of use. Data gathered through this reporting are sent regularly by the MAH to ANSM that may, where relevant, modify, suspend or withdraw the RTU. The law provides also that MAHs contribute to the correct use of their products, that is, they monitor prescriptions' adherence to MA to the temporary use authorization (ATU) or to the RTU. When companies are aware of an off label prescription of one of their medicines, they have to take appropriate measures to inform professionals and they have to inform the ANSM immediately. On June 29, 2016 the State Council rejected a request by Novartis, Roche and the French Union of the pharmaceutical industry to amend the rules relating to the preparation of temporary use recommendations as established under section I of Article L. 5121-12-1 of the Code of Public Health. As stated in section 4.4.3.1, in its 24th February 2017 decision, the Conseil d'Etat dismissed the applications brought by Roche and Novartis seeking to revoke the 24th of June 2014 decision of the National Agency for Medicines and Health Products safety recommendation to treat patients with neovascular age-related macular degeneration.

The French stakeholders who filled out the interview questionnaire for this study mentioned the following barriers for the RTU:

- The reluctance or refusal of some MAH to implement the patients follow-up;
- The reluctance of physicians to include patients into the RTU because of the weight of the tasks linked to the reporting.

Hungary

(Information source: interviewees regulatory and reimbursement Hungary)

In Hungary, in 2008 a regulation was introduced regarding the authorisation of off-label prescribing (*source: interviews with Hungarian regulators*). Based on article 25 of Act XCV of 2005 on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products (subsection 6) a medicinal product may be prescribed and used otherwise than for the authorized indications contained in the summary of product characteristics, only if:

- treatment of a patient with another authorized medicinal product is not possible or unsuccessful according to the SmPC, and based on the experimental evidence defined in specific other legislation, administering the medicinal product for an unauthorized indication offers the potential of successful treatment, or to improve or stabilize the patient's condition;
- the medicinal product in question is authorized for distribution in the Republic of Hungary or in another country; and
- the doctor specializing in the specific therapeutic area has requested individual authorization from the government body for pharmaceuticals for using the medicinal product for an unauthorized indication for the specific patient under the relevant conditions set out in specific other legislation, and the government body for pharmaceuticals has granted such authorization.



In addition, a medicinal product may be prescribed and/or used for an unauthorized indication if:

- access to a medicinal product with marketing authorization for a specific indication is inhibited to an extent that would likely delay the treatment of the patient, hence causing disproportionately great risk of irreversible health impairment, or
- the risk/benefit balance of the medicinal product prescribed for an unauthorized indication is better than that of the medicinal product with marketing authorization for a specific indication, and based on the experimental evidence defined in the relevant legislation, administering the medicinal product in an unauthorized indication offers the potential of successful treatment, and/or to improve or stabilize the patient's condition, and the conditions set out in Paragraphs b)-c) of Subsection (6) are satisfied;
- the SmPC of the marketing authorization of a medicinal product does not contain contra-indication regarding the requested unauthorized indication.

The idea behind the Hungarian legal framework is that it creates the opportunity to apply the results of research immediately. To this end, Hungary established a committee to evaluate the requests. Once permission is granted, it is valid for all patients with the same condition. Reimbursement is not seen as a crucial element in this process. The Hungarian interviewee stated that the legal tool is regarded as very useful, especially in paediatrics, oncology or in orphan diseases. On the other hand it poses a significant administrative burden for physicians and the authority.

Italy

(Information source: interviewees regulatory Italy)

In Italy, Off-label use of medicinal products is possible according to national Law n. 94/98 (the so-called Di Bella law), related to off-label use of authorised medicinal products under the personal responsibility of the prescribing physician and 648/96 national Law, when:

- there are some therapeutic areas with an unmet medical need and
- companies do not want to perform clinical trials for a given indication.

Off-label use requires the support of phase II completed study. Patient consent is also a precondition (Article 3 of Law Decree 23 of 17/02/1998). In case of application of law 648/96 the off-label use is reimbursed. The Italian stakeholder interviewed for this study stated that while the existing tools are more than adequate to address any potential need, the lack of systematic monitoring in time might be a weakness. Therefore, the Italian authority, AIFA, would like to develop a new system to better monitor efficacy and safety data regarding the use of off-label use and try to connect specific registers.

Spain

(source: interviewees regulatory Spain).

In 2009, Spain adopted specific legislation on off-label use of medicines. Before 2009 regulation, there were no specific instructions regarding off-label use. In general, for medicines under data protection or patent period, the same rules applied as did for compassionate use applied. By the time the 2009 regulation was drafted, it was considered that this process imposed an excessive bureaucracy around off-label use with little (if any) impact on scientific knowledge about these uses and an unnecessary delay for patients to achieve the treatment. The national Royal Decree No. 1015/2009 states that off-label use has to be exceptional and only limited to those situations in which no approved alternatives exist, with respect to any restriction of the conditions for prescribing and dispensing established in the authorization (i.e. hospital medicine only) and the therapeutic protocol of the centre. Physicians have to adequately justify



the need for treatment in the clinical history of the patients and inform them of the potential benefits and risks, obtaining their informed consent according to the national legislation. Off label use of medicinal products is not only allowed in the hospital setting but also in other healthcare settings such as primary care (*source: quoted from questionnaire Spanish regulatory stakeholder*). As such, no case by case authorisation for off-label use is required anymore (this is a relevant change from the former legislation).

Although authorisation is not needed, the Spanish Agency may establish therapeutic protocols and/or recommendations for the use (or not use) of medicines for conditions different to those authorised. These recommendations may be established when a risk to patients may be reasonably expected from the use in off-label conditions, when medicinal products are subjected to restricted medical prescription, or when off-label use may result in a significant healthcare impact. Examples include recommendations for the non-use of growth hormone in the recovery of brain and peripheral neurological diseases.

According to the Spanish regulatory stakeholder who was the informant for our study, the regulation imposes several obligations on the Agency, the prescribing physician and the marketing authorization holder (MAH). The Agency should set up and review recommendations for use (or non-use), maintain a system for exchanging information with the regional authorities and inform the MAH about the recommendations of use and the suspected adverse reactions (ADR) notified to the Agency. Physician's responsibilities include providing the adequate information to the eligible patients, to notify any suspected ADR according to the national legislation, and to comply with the recommendations and therapeutic protocols established. Finally, the MAH should notify any suspected ADR, to avoid any promotional activity of the off-label use of the medicine and to provide to the Agency any information related with this off-label use that may have any impact on the recommendations.

After the regulation came in place after 2009, the down-regulation of the process has been partially achieved. However, regional authorities have put internal procedures in place for off-label use, especially for new, expensive medicines due to concerns on the budget impact of off-label use. Thus, therapeutics committees of hospitals perform an evaluation of individual cases and the medical director of each hospital must give individual authorization for each patient. There are no rules for reimbursement in the Spanish regulation. Although theoretically, off-label use is not reimbursed, in practice, it is

Measures to regulate reimbursement

France and Italy both explicitly allow for reimbursement of off-label use if other (on-label/authorised) alternatives exist; requirements for off-label use are in place (see above).

Germany

(Sources: KCE, interviewee German regulatory stakeholder, German EMACOLEX member).

In Germany, expert commissions for off-label-use have been established within the national medicines agency (Federal Institute for Drugs and Medical Devices, BfArM), evaluating the current scientific knowledge about the off-label-use of specific medicinal products for specific indications.^{zzz} At present, Germany has off-label expert commissions in the fields of oncology, neurology/psychiatry, and internal medicine.

^{zzz} Legal basis: Section 35c para (1) of the German Social Code Book V (SGB V)



The law stipulates that off-label evaluations need consent of the respective pharmaceutical company / MAH. Evaluations by the off-label expert commissions may be solicited either by the Federal Ministry of Health or by the Federal Joint Committee (G-BA). The G-BA is the highest decision-making body issuing directives for the benefit catalogue of the statutory health insurance funds (GKV) and thus specifying the benefits to be reimbursed. The scientific evaluations by the off-label expert commissions are transmitted to the G-BA as a recommendation for the G-BA directive about medicinal products subject to reimbursement by the GKV. The directive then is decided upon by the G-BA according to section 92 para (1) Nr. 6 SGB V. In 2005, a ruling of the Bundesverfassungsgericht strengthened the grounds for reimbursement of off-label prescribing. According to this ruling, the costs for off-label use should also be refunded if there are only weak references for efficacy, on condition that the patient suffers from a life threatening condition and alternatives are missing (

Greece

(source: interviewee independent expert Greece)

In Greece, a ministerial decree is required for physicians to prescribe off-label. This regulation is put in place for reasons of reimbursement. Medicines are only reimbursed for their approved indications, as defined in the marketing authorisation (Law 3816/2010; Official Gazette A 6/26.10.2010). However, a subsequent Ministerial Decree (Official Gazette 545/B'/01-03-2012) regulates that for special cases and according to international bibliographic references, full applications for reimbursement can be submitted by hospitals, the National Organisation for Health Policy Provision (EOPYY) and other Social Security Funds. After their positive opinion, administration and reimbursement of the respective prescriptions is possible. Additionally, law 4316/2014 states that off-label indications could be reimbursed if included in therapeutic protocols approved by the Central Committee of Health Council (KESY). Yet, for the application a ministerial Decree is needed (no publication yet)

Hungary

(source: interviewees regulatory and reimbursement Hungary).

Another reimbursement-related policy tool is the case-by-case evaluation in Hungary. Hungary looks at each individual off-label use, as with the permission to prescribe off-label. Decisions are taken based upon circumstances (including existing alternatives and reasons why these alternatives are not sufficient) and costs of the individual treatment and within the limits of its budget. In the Netherlands, the effectiveness of the product is leading in the reimbursement decision, as it is for on-label products

(source: Hungarian regulatory stakeholder interviews).

Policy tools providing guidance to professionals

Lithuania, Sweden and the United Kingdom have policy tools in place to guide professionals in off-label prescribing. Lithuania has a regulation that describes how to use products off-label, how the doctor should act in these situations, and what documents they need to complete *(source: interviewee Lithuania, regulatory & reimbursement)*. In Sweden, if there is sufficient scientific evidence and clinical experience, off-label use is allowed and the responsibility lies mainly on the physician in his/her professional role *(source: comment Swedish stakeholder on report)*.

In the UK, the following prescribing hierarchy is in place:

- (1) use a licensed product (marketing authorisation by MHRA),
- (2) use a licensed product off-label if needed (guidance by General Medical Council; the UK regulatory authority for medical professionals)
- (3) use a non-licensed product.



When prescribing an unlicensed medicine (which includes off-label use) a prescriber “must be convinced that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy. Also, the prescriber needs to take responsibility for prescribing the medicine and for overseeing the patient’s care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so. Also, the prescribers need to have a clear, accurate and legible record of all medicines prescribed and the reasons for prescribing a medicine off-label (Good practice in prescribing and managing medicines and devices, 2013) (source: *interviewees regulatory UK*).

Policy tools where professional standards are leading

The Netherlands has a policy tool in place where professional standards are leading in off-label use: off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use. If protocols or standards are still under development, the physician and the pharmacist are required to consult each other (source: *interviewees regulatory and reimbursement Netherlands*).

Policy tools focussing on the patient

Informed consent of the patient is a requirement in France, Italy, the Netherlands, Sweden and the UK^{aaaa} (source: *interviewees from regulatory stakeholders from the respective countries*). In the Netherlands, the law includes a provision in case the patient needs an intensive intervention. Article 451 of the Civil Code states that, upon request of the patient, the HCP has to register (in written form) for what intensive treatment interventions the patient has given informed consent (source: *interviewees regulatory and reimbursement Netherlands*). Spain mentions to regulate what information has to be given (as is the case for on-label use) (source: *interviewees regulatory Spain*).

Future plans

Starting in 2017, Dutch HCPs need to register the indication when they prescribe a category of expensive medicines to patients (both authorized and off-label indications) (source: *interviewees regulatory and reimbursement Netherlands*). This improves the transparency, effectiveness, accessibility, quality, supervision and the legal viability of regulation on medicines.^{bbbb} Other Member States discuss potential changes. In Hungary, ideas to simplify the current system to get permission are being discussed, for example waiving the requirement for permission in case of emergency situations and to simplify the process of asking for permission (source: *interview regulatory and reimbursement Hungary*). In the UK, a few members of the parliament asked the Secretary of State to take responsibility for obtaining new licenses for off-patent drugs but the Bill (draft law) did not come any further. Moreover, there is a lot of attention for repurposing of medicines (old drugs with new indications) in the UK (source: *interviewee regulatory UK*). Spain debates the rules for reimbursement (there is nothing in place right now in Spain) and new models of authorisation. An example of such model, discussed in the EU in a broader context than off-label use, is the use of adaptive pathways. EMA defines adaptive pathways as: “scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine”.^{cccc} It is based on three principles: iterative development of medicines, gathering evidence through real-life use to supplement clinical trial data and early involvement of patients and health-technology-assessment bodies in discussions on a medicine’s development. Adaptive pathways is primarily meant for

^{aaaa} It may well be that informed consent is requested in more countries but it was not mentioned specifically during the interviews

^{bbbb} https://www.nza.nl/1048076/1048107/CI_16_28c__Regelgeving_2017_add_on_geneesmiddelen_en_ozp_stollingsfactoren.pdf

^{cccc} http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp



treatments in areas of high medical need where data on evidence are not easily being collected via traditional routes. The standards for risk-benefit evaluation are the same as for other products and the approach builds on regulatory processes already in place within the existing EU legal framework.^{dddd} Adaptive pathways might stimulate MAHs to register their products for more indications, as such reducing the chance of off-label use (source: interviewee regulatory Spain).

Ways to identify off-label use

Some Member States with policy tools in place do not have systems in place that are suitable to identify off-label use. Other countries have databases that could be used to identify off-label use. In some countries these databases are indeed used for off-label purposes (e.g. Greece, Lithuania, and Spain) but in other countries they are not. A UK representative stated that although technically this information could be retrieved, there is a lot of controversy in the UK on the use of clinical information. Hungary has a different database, namely a national database (published by the National Institute of Pharmacy and Nutrition), where all requests for off-label prescribing are registered (source: reimbursement: Lithuania; regulatory Hungary, Spain and UK; independent expert: Greece)

In all Member States, adverse events should be reported in accordance with the EU Pharmacovigilance legislation, as it should be done for on-label use. Some countries have extra services. One example is the UK, where the MHRA has a system in place for adverse drug reactions: the "Yellow card" system which can also be filled in by patients, and family members of patients to report side effects, which could concern off-label use. Also Ireland operates a "Yellow Card system"^{eeee} (source: interviewees regulatory Ireland and UK).

^{dddd} http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp

^{eeee} Other countries may have such systems in place as well, but these were not mentioned during the interviews.



Table 4.4: Summary of policy tools addressing off-label use in nine EU Member States derived from the interviews

France	<p><i>Policy tool (regulatory & reimbursement): Temporary recommendations for use (RTU) scheme</i></p> <p>A temporary recommendations for use (RTU) scheme is in use. The RTU-system is set up at the initiative of the ANSM (French regulator). ANSM informs the marketing authorisation holder (MAH) about the need of a RTU and asks the MAH to provide all available data on the concerned indication. The RTU can be notified, in accordance with the European Court of Justice court case law to fulfil special needs, if the benefit/risk ratio of the medicinal product is presumed to be favourable, in situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product should be administered, and for which there is no alternative medicinal product with the same active substance, the same dosage and the same form. The objectives of the RTU are to make off-label use safer as patients should be monitored through a protocol, to improve knowledge regarding efficacy and safety of off label use, and to encourage the pharmaceutical companies to file for an MA extension. A medicine covered by a RTU can be reimbursed by the national health insurance. The prescriber has to inform the patient of the off label use and of the potential benefits and risks attendant to the use. The temporary recommendations for use (RTU) were introduced December 29 2011 (the n° 2011-2012 act). (see text for more information).</p> <p><i>Policy tool (reimbursement): Allowing off-label use when there are alternatives on the market</i></p> <p>While the RTU was restricted to situations with a lack of alternative treatments, the scheme has been extended to situations where alternative – but not strictly identical – treatments exist.</p> <p>Links, information on RTU: http://ansm.sante.fr/Activites/Recommandations-Temporaires-d-Utilisation-RTU/Les-Recommandations-Temporaires-d-Utilisation-Principes-generaux/%28offset%29/0 http://ansm.sante.fr/var/ansm_site/storage/original/application/bd8ccb71932937accccb61fdf15a82ff.pdf</p>
Germany	<p><i>Policy tool (reimbursement): Commissions evaluating knowledge on which the competent authorities decide on reimbursement</i></p> <p>Commissions for off-label-use (for oncology, neurology/psychiatry, and internal medicine) have been established within the national medicines agency (Federal Institute for Drugs and Medical Devices, BfArM), evaluating the current scientific knowledge about the off-label-use of specific medicinal products for specific indications. The law stipulates that off-label evaluations need consent of the respective pharmaceutical company / marketing authorisation holder. Evaluations by the off-label expert commissions may be solicited either by the Federal Ministry of Health or by the Federal Joint Committee (G-BA). The G-BA is the highest decision-making body issuing directives for the benefit catalogue of the statutory health insurance funds (GKV) and thus specifying the benefits to be reimbursed. The scientific evaluations by the off-label expert commissions are transmitted to the G-BA as a recommendation for the G-BA directive about medicinal products subject to reimbursement by the GKV. The directive then is decided upon by the G-BA according to section 92 para (1) Nr. 6 SGB V.</p> <p>Link: https://www.g-ba.de/institution/themenschwerpunkte/arzneimittel/off-label-use/</p>
Greece	<p><i>Policy tool (reimbursement): Permission request for off-label use</i></p> <p>Medicines are only reimbursed for their approved indications, as defined in the marketing authorisation (Law 3816/2010; Official Gazette A 6/26.10.2010). However, a subsequent Ministerial Decree (Official Gazette 545/B' /01-03-2012) regulates that for special cases and according to international bibliographic references, full applications for reimbursement can be submitted by hospitals, the National Organisation for Health Policy Provision (EOPYY) and other Social Security Funds. After their positive opinion, administration and reimbursement of the respective prescriptions is possible.</p> <p>Additionally, law 4316/2014 states that off-label indications could be reimbursed if included in therapeutic protocols approved by the Central Committee of Health Council (KESY). Yet, for the application a ministerial Decree is needed (no publication yet).</p>



	<p>Links: https://www.taxheaven.gr/laws/law/index/law/163 https://www.taxheaven.gr/laws/circular/view/id/13687</p>
Hungary	<p>Policy tool (regulatory): Permission request for off-label use Off-label use of any medicinal product is subject to specific, individual authorisation of the HTA Committee and the National Institute for Quality and Organisational Development in Healthcare and Medicines. It is granted upon the request of the prescriber.</p> <p>For off-label use of medicines physicians need to apply for a permission (an application licence) at the National Institute of Pharmacy and Nutrition and the HTA Committee. Once permission has been provided, this will be published. For an off-label use covered by published permissions or by healthcare professionals' protocols a simplified application for permission may be submitted.</p> <p>Discussions on reform of the system (applying for permission to prescribe off-label) just started. These focus on the process of getting permission as well as on the exemption of some types of products/ off-label uses from permission applications, for example in situations of emergency.</p> <p>Policy tool (reimbursement): Case-by-case evaluation Reimbursement can take place on a case-by-case basis. The Health Insurance Fund must take the decision based upon circumstances and costs of the individual treatment and within the limits of its budget. In case there are alternatives this should be taken into account alongside the reasons why these alternatives are not suitable for treatment of the patient.</p> <p>Links: http://www.ogyei.gov.hu/listak/ (public records of all authorised off-label uses) http://ogyei.gov.hu/swf/gyogyszereink/61_4/files/2011_4_final_web.pdf (article on "Evaluation of the off-label authorization process based on the published database of the National Institute of Pharmacy")</p>
Italy	<p>Policy tool (regulatory and reimbursement): Legal framework for off-label use Off-label use of medicinal products is possible according to national Law n. 94/98 (the so-called Di Bella law), related to off-label use of authorised medicinal products under the personal responsibility of the prescribing physician and 648/96 national Law, when:</p> <ul style="list-style-type: none"> - there are some therapeutic areas with an unmet medical need and - companies do not want to perform clinical trials for a given indication. <p>Off-label use requires the support of phase II completed study. Patient consent is also a precondition (Article 3 of Law Decree 23 of 17/02/1998). In case of application of law 648/96 the off-label use is reimbursed.</p> <p>Policy tool (reimbursement): Allowing off-label use when there are alternatives on the market Law 79/2014 has introduced the possibility of reimbursement of off-label indications for which there are already alternatives on the market, provided that it is supported by robust scientific data and a proper assessment of economic appropriateness has been performed. Since 2014, Italy has introduced a new law that allows reimbursement of off-label prescribed but cheaper equivalents of medicines.</p> <p>Link: http://www.aifa.gov.it/en</p>
Lithuania	<p>Policy tool (regulatory and reimbursement): Regulating how to put off-label use in practice There is a regulation that describes how to use products off-label, how the doctor should act in these situations, and what documents they need to complete. Orders of the minister of health regulate that patients can be treated with a product that is not registered. The order also regulates the reimbursement of the product.</p>
Netherlands	<p>Policy tool (regulatory): regulating through professional standards In the Netherlands, Article 68 of the Medicines Act provides that off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use. If protocols or standards are still under development, the physician and the pharmacist are required to consult each other.</p>



	<p>Policy tool (regulatory): informed consent At the request of the patient, a health care worker has to document (in writing) for what significant treatments the patient has given consent (art. 451 Civil Law).</p> <p>Policy tool (regulatory): registration of indications New: The Netherlands has a new regulation under development that states that as of 2017 healthcare professionals need to register the indication on the reimbursement form when they prescribe a category of expensive medicines to patients (both registered and off-label indications). Patients can sign an opt out form.</p> <p>Link: https://addon2017.files.wordpress.com/2016/03/handreiking-e28098wijzigingen-add-on-geneesmiddelen-2017_.pdf.</p>
Spain	<p>Policy tool (regulatory): Regulating requirements for off-label use In 2009, Spain adopted specific legislation on off-label use of medicines. This regulation formally sets out the requirements of necessity (lack of an authorized alternative), a scientific basis and informed consent. This royal decree established that off-label use:</p> <ul style="list-style-type: none"> - has to be exceptional and limited to those situations where no approved alternatives exist; - with respect to any restriction of the conditions for prescribing and dispensing established in the authorisation (i.e., hospital medicine only) and - the therapeutic protocol of the centre. <p>Policy tool (regulatory): Regulating patient information Physicians have to adequately justify the need for treatment in the clinical history of the patients and inform them of the potential benefits and risks, obtaining their informed consent according to the national legislation.</p> <p>Link: http://www.boe.es/boe/dias/2009/07/20/pdfs/BOE-A-2009-12002.pdf</p>
Sweden	<p>Policy tool (regulatory): informed consent Any therapeutic intervention, (including prescribing on- or off-label), should be based on scientific and clinical experience and the patient should be consulted and give consent (Patient safety legislation SFS 2010: 659, Patient legislation SFS 2014:821).</p> <p>Policy tool (regulatory): Guidance for prescribers At the local level and by national law drug committees recommend and follow up on prescribing patterns, and the HSCI monitors prescribing, including off-label.</p> <p>Links: https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/patientsakerhetslag-2010659_sfs-2010-659 http://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/patientlag-2014821_sfs-2014-821</p>
United Kingdom	<p>Policy tool (regulatory): Prescribing hierarchy The UK has so-called 'soft law', using a prescribing hierarchy: (1) use a licensed product (marketing authorisation by MHRA), (2) use a licensed product off-label if needed (guidance by General Medical Council; the UK regulatory authority for medical professionals) (3) use a non-licensed product.</p> <p>Policy tool (regulatory): Guidance for prescribers The GMC Guidance (Good practice in prescribing and managing medicines and devices, 2013) indicates that when prescribing an unlicensed medicine (which includes off-label use) a prescriber "must:</p> <ul style="list-style-type: none"> - be convinced that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy; - take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so; - make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine." <p>NICE publishes specific guidance documents, i.e. evidence summaries for unlicensed or</p>



	off-label used medicines. Links: http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp http://www.nice.org.uk/advice?type=esum
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4.6 Stakeholder opinions on off-label use

Key findings on stakeholder opinions on off-label use

- A major advantage of off-label use – according to all types of stakeholders - is the better access of patients to – innovative – treatments and the fulfilment of medical needs of patients, especially in cases where no other options are available.
- Another positive element mentioned mainly by regulators and policy makers in the field of reimbursement is the potential economic advantage: off-label use contributes to sustainability of the healthcare system. However, stakeholders also see disadvantages when economic reasons are prevailing, such as friction between national authorities and the pharmaceutical industry.
- The issue of liability in case of negative consequences of off-label use is a concern for many stakeholders from different backgrounds.

In this section, we describe the stakeholders' views on off-label use: what do they consider advantages and disadvantages? These views are important to understand the position of different stakeholders with regard to the acceptance of (potential) policy options which will be discussed in section 4.6. These views were discussed during the interviews with representatives of EU Member States and EU-level stakeholders (see chapter 2.4.1 for more information).

4.6.1 Regulatory level

At the regulatory level, three major areas were addressed where (all or some) stakeholders saw potential negative aspects of off-label use: liability, undermining the market authorisation process and discouragement of R&D.

Liability

A broadly held concern among all types of stakeholders is that responsibility in case of adverse events, is not always clear (*source: interviewees* regulatory: Belgium, Denmark, Finland, France, Hungary, Italy, Portugal, Slovenia, Spain, Sweden; reimbursement: Slovenia; independent expert: Bulgaria, Greece, Malta; patient organisation: Irish premature babies; professional organisation: EAHP; industry: EUCOPE). Stakeholders consider this as a major disadvantage of off-label use as it puts responsibility on prescribers. Important in this regard is the lack of information on the benefit-risk ratio of off-label uses. The Belgian KCE-report concluded that off-label use is not prohibited as such but that off-label use of medicines “*could raise liability questions for manufacturers (product liability), practitioners, pharmacists and public health authorities*”.⁵ Manufacturers risk to be held liable in case they promote off-label use; promotion of off-label prescribing is prohibited. They can also be held liable in case they “*omit to warn for possible adverse reactions in association with an off-label indication*”⁵.



Undermining the market authorisation process

Another argument against off-label use mentioned by stakeholders of various backgrounds (*source: interviewees regulatory: Netherlands, Portugal; reimbursement: Netherlands; independent expert: Bulgaria; patient organisation: EAASM, Irish Premature Babies*), is undermining of the market authorisation process and the potential loss of control and trust in the regulatory system as well as in the approved medicines. This is, according to stakeholders from EU-level pharmaceutical organisation EFPIA, the case when economic off-label use promotion happens by national healthcare systems. It was also stated that off-label use should not be a way to 'easy marketing' (i.e. the requirements for marketing authorisation need not to be fulfilled; the product is used anyway).

Discouragement of R&D

Widespread off-label use can also discourage R&D, including clinical trials, as there is no incentive to do R&D (the product is prescribed off-label anyhow) (*source: interviewees regulatory: Portugal and Sweden; patient organisation: EAASM, Irish Premature Babies*).

4.6.2 Healthcare system level

Potential economic advantages of off-label use are considered to be an advantage for the healthcare system by a wide variety of stakeholders (*source: interviewees regulatory: Belgium, Finland, Hungary, Ireland, Netherlands Portugal, Spain, Sweden; reimbursement: Netherlands; independent expert: Bulgaria, Czech Republic; patient organisation: EAASM, IAPO, Irish premature babies*). An example that is often mentioned in this regard is the Avastin® / Lucentis® case, where the off-label product is cheaper than the on-label product which can save costs for health care. This may lead to better access to medicines: patients have access to a medicine for their disease that otherwise would not have been available or affordable either for the individual patient or for the healthcare system as a whole (*source: interviewees regulatory: Hungary, Portugal, Spain, Sweden; patient organisation: IAPO; professional organisation: UEMS*). As such, off-label use may contribute to sustainability of the healthcare system. Moreover, for small countries off-label use contributes to the fact that patients have better access to treatments, because fewer medicines are on their market and shortages in treatment options can be avoided (*source: interviewees reimbursement: Lithuania; independent expert: Estonia*).

Yet, not all stakeholders evaluate economic advantages as merely positive. The cost-effectiveness is, for example, unknown (*source: interviewee expert: Estonia*). Reimbursement issues may put pressure on the relationship between some national authorities and the pharmaceutical industry (*source: interviewees independent expert: Malta; industry: EFPIA*). This is the case when authorities reimburse off-label use in case the off-label product is cheaper compared to the authorized product. In addition, reimbursement issues can put the relationship between patients and prescribers on the one hand and payers on the other hand at stake. Such situation can occur if the payer refuses to reimburse an off-label treatment. Off-label use can lead to problems for patients and practitioners for example when they have to negotiate with health care insurers whether or not the prescription will be reimbursed (*source: interviewees independent expert: from the Czech Republic*) or when it is uncertain whether or not the off-label use is not reimbursed (*source: interviewees regulatory: Finland and Germany*).

Another issue is that – both at the regulatory and the healthcare system level – in case off-label use would be subject to strict regulation, mechanisms to reinforce that prescribers obey to this regulation will be hard to be put in place (*source: interviewees regulatory: Spain*).



4.6.3 Patient and health care professional level

At the patient and health care professional level two areas were addressed where all or some of the stakeholders saw potential positives aspects of off-label use: the increased availability of treatments to meet medical needs of patients and, related to that, better access to medicine. There were also several areas where they saw potential negative aspects of off-label use (see below).

Better access and fulfilment of medical needs

The main and most widely supported advantage of off-label use by all types of stakeholders is the better access of patients to – innovative – treatments and the fact that medical needs of patients can be fulfilled, especially for patients whose needs otherwise could not have been met (source: interviewees regulatory: Austria, Belgium, Denmark, France, Germany Hungary, Ireland, Italy, Netherlands, Portugal, Slovenia, Spain, Sweden, UK, EMA; reimbursement: Lithuania, Netherlands, Slovenia; independent expert: Bulgaria, Czech Republic, Greece, Malta; patient organisations: EAASM, EURODIS, Irish premature babies; professional organisations: EHA, UEMS; industry: EFPIA, EUCOPE). For prescribers off-label this means that they have more treatment options to choose from in order to provide a treatment they find most suitable for the needs of a particular patient. In addition, because of off-label use access to medicines is better, especially in small markets where fewer medicines are available (source: interviewees regulatory: Hungary; independent expert: Estonia). Moreover, off-label drugs can be more convenient for the patient, for example because the route of administration better suits the patient needs (source: interviewees regulatory: Sweden). Off-label prescribing also makes medicines available to more patient cohorts at an earlier stage, based on the newest scientific evidence available, before the required (long taking) regulatory approval (source: interviewees regulatory: Spain, Sweden, UK; independent expert: Estonia).

Lack of information on benefit-risk balance in choice of treatment

A disadvantage of off-label use, mentioned by all types of stakeholders, is the more limited amount of information on the benefit-risk balance on which the prescriber has to base the treatment choice be fulfilled, especially for patients whose needs otherwise could not have been met (source: interviewees regulatory: Austria, Belgium, Denmark, France, Germany, Hungary, Ireland, Italy, Portugal, Slovenia, Spain, Sweden, UK, EMA; reimbursement: Hungary, Lithuania, Slovenia; independent expert: Czech Republic, Estonia, Greece; patient organisations: Irish premature babies; industry: EUCOPE). Related to this is the argument that studies are often of lower quality than those that are used for official registration (source: interviewees regulatory: Austria, Italy, professional organisations: UEMS; industry: EFPIA). This may potentially give increased risk for adverse events for the patient (source: interviewees regulatory: Hungary, Ireland, Italy, Sweden; reimbursement: Lithuania; independent expert: Bulgaria, Czech republic, Greece; patient organisations: EAASM, EURODIS; professional organisations: EAHP, EHA). In case of off-label prescribing patients have less information to their disposal to decide on whether or not they will accept the treatment (source: interviewees regulatory: Denmark, Ireland, Italy, Portugal, Spain; expert: Bulgaria, Estonia; patient organisations: EURODIS; industry: EUCOPE). Not only can prescribers offer them less information on risks and benefits of the treatment, there is also a lack of regulated patient information. Also, lack of guidelines can be problematic (source: interviewee independent expert: Malta; professional organisations: UEMS). Yet, some stakeholders stated that, if properly documented, off-label use can contribute to the level of knowledge on medicines (source: interviewees regulatory: Hungary, Sweden; independent expert: Bulgaria). The more limited amount of information on the benefit-risk balance also has implications for the previously mentioned issue of liability, as doctors are responsible for off-label prescribing as well as for informing the patient about off-label use (source: see above paragraph on liability). With regard to pharmacists, it should be mentioned that in many Member States the



indication for which a medicine has been prescribed is unknown for pharmacists. This hampers them in evaluating the safety of an off-label product (*source: interviewee professional organisations: PGEU*).

4.6.4 Views per stakeholder group

In this section, the opinions as mentioned in the previous sub-sections are grouped according to type of stakeholder. This is done in order to be able to distinguish between the views of different types of stakeholders. Only the most frequently mentioned factors are summarized.^{ffff}

Regulatory and reimbursement stakeholders

- Regulatory level: Part of the interviewed stakeholders in this group mentioned to be concerned about the fact that when using a medicine off-label, it is not clear who is responsible in case of adverse events (*Belgium, Denmark, Finland, France, Hungary, Ireland, Italy, Portugal, Slovenia, Spain, Sweden*).
- Health system level: Potential economic advantages of off-label use for the health care system are mentioned as an advantage for the healthcare system by a number of stakeholders in this group (*Belgium, Finland, Hungary, Ireland, Netherlands Portugal, Spain, Sweden*). This may lead to better access to medicines: patients have access to a medicine for their disease that otherwise would not have been available or affordable either for the individual patient or for the healthcare system as a whole (*Hungary, Portugal, Spain, Sweden*).
- Professional and patient level: Because of off-label use there is better access of patients to – innovative – treatments and the fact that unmet medical needs of patients can be fulfilled (*Austria, Belgium, Denmark, France, Germany Hungary, Ireland, Italy, Netherlands, Portugal, Slovenia, Spain, Sweden, UK, EMA*).
- Professional and patient level: According to some of the stakeholders in this group, off-label prescribing also makes medicines available to more patient cohorts at an earlier stage (*Spain, Sweden, UK*).
- Professional and patient level: Another downside to off-label use for both patients and prescribers is the more limited amount of information that is available on the benefit-risk balance on which the prescriber has to base the treatment choice and the patient has to decide whether or not to accept the treatment (*Austria, Belgium, Denmark, France, Germany, Hungary, Ireland, Italy, Portugal, Slovenia, Spain, Sweden, UK, EMA*). This may potentially lead to an increased risk for adverse events for the patient (*Hungary, Ireland, Italy, Lithuania, Sweden*).

Independent experts

- Regulatory level: Part of the interviewed stakeholders in this group mentioned to be concerned about the fact that when using a medicine off-label, the responsibility in case of adverse events is not always clear (*Bulgaria, Greece, Malta*).
- Health system level: Potential economic advantages of off-label use for the health care system are considered to be an advantage for the healthcare system by a number of stakeholders in this group (*Bulgaria, Czech Republic*).
- Professional and patient level: The main and most widely supported advantage of off-label use is the better access of patients to – innovative – treatments and the fact that unmet medical needs of patients can be fulfilled (*Bulgaria, Czech Republic, Greece, Malta*).

^{ffff} It also depends on the size of the stakeholder group whether an argument is considered as a main argument as in some stakeholder groups less interviews have been performed.



- Professional and patient level: A downside to off-label use for both patients and prescribers is the more limited amount of information that is available on the benefit-risk balance on which the prescriber has to base the treatment choice and the patient has to decide whether or not to accept the treatment (*Czech Republic, Estonia, Greece*).

Patient organisations

- Health system level: Potential economic advantages of off-label use for the health care system are considered to be an advantage for the healthcare system by a number of stakeholders in this group (*EAASM, IAPO, Irish premature babies*).
- Professional and patient level: The main and most widely supported advantage of off-label use is the better access of patients to – innovative – treatments and the fact that unmet medical needs of patients can be fulfilled (*EAASM, EURODIS, Irish premature babies*).
- Professional and patient level: A downside to off-label use for both patients and prescribers is the more limited amount of information that is available on the benefit-risk balance on which the prescriber has to base the treatment choice and the patient has to decide whether or not to accept the treatment (*EAASM, EURODIS*). This may potentially lead to an increased risk for adverse events for the patient (*EAASM, EURODIS*).

Professional organisations

The opinions of the professional organisations are diverse. All but one opinions in sections 4.6.1 to 4.6.3 were mentioned by only one organisation. The exception was the fact that off-label use may potentially lead to an increased risk for adverse events for the patient (*EAHP, EHA*).

Industry

- Regulatory level: *EUCOPE* was concerned about the fact that when using a medicine off-label, the responsibility in case of adverse events is not always clear.
- Health system level: *EFPIA* refers to the fact that reimbursement issues may put pressure on the relationship between some national authorities and the pharmaceutical industry.
- Professional and patient level: Both *EFPIA* and *EUCOPE* find that off-label use can provide better access of patients to – innovative – treatments and the fact that unmet medical needs of patients can be fulfilled.
- Professional and patient level: Another downside to off-label use for both patients and prescribers is the more limited amount of information that is available on the benefit-risk balance on which the prescriber has to base the treatment choice and the patient has to decide whether or not to accept the treatment (*EUCOPE*). This information may come from studies that are often of lower quality than those that are used for official registration (*EFPIA*).

4.7 Policy options: report of the stakeholder meeting

An expert meeting was held in order to have a synthesis of pros and cons of off-label use. Representatives from Member States who are responsible for authorising and controlling the use of the medicinal products, and/or are responsible for pricing and reimbursement, were asked to participate. Also, we invited representatives of EU-level stakeholder organisations (patient organisations, organisations of prescribers and pharmacists and pharmaceutical industry). A total of 19 persons participated in the



meeting (See Table B.2 in Annex B and section 2.4.2). These experts discussed the pros and cons of different policy tools.

The following policy tools are currently in place in EU Member States (see section 4.4):

- Legal frameworks to issue temporary recommendations for use and permission to prescribe off-label;
- Measures to regulate reimbursement;
- Policy tools providing guidance to prescribers in off-label use;
- Policy tools where professional standards are leading for off-label use;
- Policy tools focused on the patient: patient information.

Moreover, in the interviews, areas for new policy options were mentioned. For the discussions at the expert meeting, a varied selection was made by the research team based on support by stakeholders during the interviews.

How to read this section

Pros and cons of the selected options discussed during the expert meeting with stakeholders will be described below. These statements are derived from the report of the meeting sent to the participants who gave their consent. As such we consider the report to be a consensus document. Yet, on some issues there was no agreement between the participants. This was explicitly mentioned in the report of the meeting. If this was the case, it is explicitly mentioned below as well. In case of consensus, we refer to the participants as “the stakeholders” and/or we just describe the results of the discussion. The results will be supplemented by pros and cons mentioned during the interviews about some of the options; this will be explicitly mentioned in the text.⁹⁹⁹⁹ In section 5.2, information from this section will be combined in a more thorough analysis where the stakeholders’ opinions will be combined with other information sources such as information on the regulatory framework.

4.7.1 Regulatory level

Five major areas for policy tools at the regulatory level were identified. Table 4.5 summarises the main pros and cons as provided by experts.

Regulating permission to prescribe off-label use

The first policy option is to regulate the permission to prescribe off-label as is the case in Hungary (see section 4.3). An advantage of introducing such a system is that it provides prescribers and patients with more assurance as the use is evaluated by regulators. This improves the position of the prescriber in terms of liability. Moreover, regulators and policy makers have a better insight in which products are *prescribed off-label and for which patient groups*. A *disadvantage, according to the Hungarian interviewees (regulatory and reimbursement)*, is the administrative burden a permission procedure puts on the regulatory system as many requests are made which all have to be evaluated which requires enough capacity at the regulatory office (*source: interview with regulatory authority from Hungary*). Also for prescribers it requires effort to prepare an application. For patients there is possibly a delay in the treatment (*source: regulatory authority from Germany*).

⁹⁹⁹⁹ Interviewees only mentioned pros and cons for tools and regulations in their own country.



Encouraging companies to submit requests for extension of indication by using new models such as RTU

Requests for extension of indications may be encouraged by new models such as the RTU in France. Advantages are comparable to those of the Hungarian system, for example that available information on the product is evaluated, which provides more insight in the risk-benefit balance. This may facilitate the decision made by them on the preferred treatment. During the interviews and the expert meeting it became clear that there was opposition from stakeholders from the pharmaceutical industry on one particular part of the model, being that the RTU can also be given to products where alternative on-label treatments exist.

Providing incentives for pharmaceutical companies to register new indications

This policy option refers to facilitating the extension of indications by providing incentives for pharmaceutical companies to register new indications for which the product is already used off-label or is expected to be used as such: incentives such as extended market protection / exclusivity. Examples of these are the Regulation 1901/2006/EC (Paediatric Regulation) and the Orphan drug Regulation 141/2000/EC. Advantages are that pharmaceutical companies may be stimulated to register for indications, which was the case for rare diseases. However, the expert meeting agreed that in the field of paediatric use the incentives did not have such effects (yet). Most stakeholders in the expert meeting felt that there are enough incentives in place for market authorisation holders to register their products and new indications. An exception was the stakeholder from the pharmaceutical industry who argued that incentives for the industry to register off-label indications should be addressed at the EU-level and that (special) incentives should be part of the EU regulatory framework.



Table 4.5 Main pros and cons of policy options at the regulatory level
(according to stakeholders)

Policy tool	Pro	Con
Regulating permission to prescribe off-label use (example Hungary)	Evaluation of available evidence on an off-label product by regulators	Administrative burden to ask for permission for prescribers
	Potentially less problems with regard to liability as there is a legal framework for off-label use	Administrative burden for regulators / capacity needed to maintain the system
	Better overview of which products are prescribed off-label and for which patient groups	Administrative burden for enforcement of compliance and possible delay of treatment
Encourage companies to submit requests for extension of indications (new models such as French RTU)	Evaluation of available evidence on an off-label product by regulators	Administrative burden to ask for MAH to deliver information
	Potentially less problems with regard to liability as there is a legal framework for off-label use	Might lead to discussion with pharmaceutical industry and ultimately to court cases
Providing incentives for pharmaceutical companies to register new indications	Might stimulate R&D activities such as in the field of rare diseases	Incentives that were established (e.g. in the paediatric field did not have strong effect yet
	Improvement of available authorised therapies	Stakeholders other than the pharmaceutical industry feel there are enough incentives in place for market authorisation holders to register their products and new indications.
Use of evidence other than industry-based RCTs – general	More information on risk-benefit balance in case of off-label use	Level of evidence is less solid
	Direct application of new scientific insights	More bias may occur as negative results may not be published
	Useful for populations with low number of patients	Stakeholders opinions are divergent on the question whether information should be included in the SmPC as Directive 2001/83 would have to be adapted for this. This is because the SmPC now is the property of the MAH
	Other parties involved in the collection of evidence, cooperation like in IMI-initiative can contribute to acquiring knowledge	
Evidence through patient registries databases with information on evidence	Enables to monitor efficacy and adverse effects of off-label use and establish whether off-label use is rational or not.	Needs to meet some important conditions such as:
	Provides evidence and enables the decision-making process in the doctor's office as more information is available.	<ul style="list-style-type: none"> Databases should be anonymous, not contain identifying information E-prescriptions are important and useful for this aim; Administrative burden for health care professionals should be limited
Use of other evidence from obligatory adverse event reporting	Contributes to knowledge on safety	Liability can be an issue in case of non-anonymous reporting
	Probably less effective than a soft approach where HCPs are convinced to report on a voluntary basis (preferably anonymous)	Reinforcement mechanisms hard to establish.
Guidelines at EU-level	Harmonisation, common ground	Treatment guidelines should be at Member State level as the context of off-label use differs across MS.
	Provides guideline developers in Member States with guidance on what to include in guidelines and on relation between guidelines and the regulatory framework at the EU-level	Differences also occur from medicine to medicine.
	Consensus among stakeholders in the expert meeting that this is useful	

*Use of evidence other than industry-based RCTs - general*

This next option is facilitating market authorisation by accepting other evidence than industry-based RCTs. This has several advantages. There is more information available on the risk-benefit balance of a product and using other data, for example real-world data, allows for direct application of new insights. This increases the scientific profile of the medicinal product. The information can be included in professional guidelines and might eventually be beneficial for the health care system. Stakeholders consider this option to be especially useful for products that are intended for small populations, such as rare diseases and paediatric conditions, where it is hard to find a sufficient number of patients for RCTs. A disadvantage is that the information is less solid and that the risk of bias might be larger than for on-label products meaning that only positive results might be published. Views of stakeholders in the stakeholder meeting were divergent with respect to the question whether this (new) information should be included in the SmPC of a product.^{hhh} Another – and by some participants in the expert meeting preferred – option would be to include this information in health care professional guidelines such as is the case in the Netherlands.

Use of evidence from patient registries and databases with information on evidence

Patient registries include information on efficacy and side effects of off-label used medicines on a patient level. Such patient registries are mainly considered to be valuable as they enable to monitor efficacy and adverse effects of off-label use and establish whether off-label use is rational or not. Stakeholders during the expert meeting stated that important conditions for registries include:

- To get the most valuable information, notifications that are valuable for databases should be anonymous and not contain patient- or practitioner identifying information as this might hamper prescribers to register information;
- E-prescriptions are important and useful for this aim;
- The administrative burden for health care professionals should be limited.

Next to registries also stakeholders in the expert meeting stated that databases with evidence on off-label use could be made available for both health care professionals and patients. Such database would enable the decision-making process in the consultation room as more information is available. As was stated in the paragraph on *use of evidence other than industry-based RCTs* there are some disadvantages as well, such as the fact that the evidence is less solid.

Use of evidence from (obligatory) adverse event reporting by HCPs

There was widespread support among stakeholders in the expert meeting that there are different amounts of recorded adverse drug events between medicines that are off-label used and those that are on-label used (lower in off-label use). This implies an imbalance which should be noted and solutions should be arrived at. However, according to stakeholders in the expert meeting, liability of doctors could be an issue in case of non-anonymous reporting and reinforcement mechanisms are hard to establish. Finally, obligatory reporting implies that a doctor knows that a prescription is off-label, which he/she is not always aware of. Therefore, stakeholders were more in favour of a soft approach (increasing awareness and confidence that reporting is necessary and helpful) and deemed this more effective.

Guidelines at the EU-level

A next option is the development of a general guideline on off-label use at the EU-level which describes the legal framework and the relation between the legal

^{hhh} Directive 2001/83 would need to be adapted for this.



framework and professional guidelines. Such general guideline could provide guidance on what elements could be included in professional standards in regard of off-label use and how professional guidelines could be developed: informed consent, various levels of evidence, information for the patient, monitoring, patient involvement in preparing guidelines. As such, it would provide a common ground for national treatment guidelines in EU Member States. The stakeholders in the expert meeting agreed that treatment guidelines themselves are preferably developed at the country level.

4.7.2 Health care system level

At the health care system level, there is one major area for policy tools: the area of pricing and reimbursement (Table 4.6). Reimbursement is regulated at the Member State level, which is supported by almost all stakeholders. Two situations can be distinguished:

1. a situation where no on-label alternative exists

In this latter situation, there is not much debate among stakeholders whether or not to reimburse the off-label product. It depends on the reimbursement rules in the respective Member States whether a product in this situation is reimbursed or not – as reimbursement is the remit of the individual Member States.

2. a situation where an on-label competitor is on the market

Reimbursement policies to regulate off-label use are clearly subject to discussion if there is an on-label competitor in the market and the off-label product is not (only) prescribed because of the medical need of the patient but because it is less expensive. Countries like France and Italy have a system where off-label prescribed products can be reimbursed even if there is an authorised alternative (but not strictly identical). Especially, the stakeholders from the pharmaceutical industry stated that off-label use is not the right platform to address high costs of medicines (e.g. Avastin® versus Lucentis®). They referred to the court case of the Commission versus Poland where the Court of Justice confirmed that financial reasons do not justify derogation from the marketing authorisation requirements. However, while all stakeholders in the expert meeting agreed that the medical need should be leading and not economic considerations, some stakeholders (*regulators, reimbursement*)ⁱⁱⁱ understood that other factors should be taken into consideration at a Member State level as well. These are factors such as budget control and sustainability of the health care system.

ⁱⁱⁱ In the report of the expert meeting no statements of individual stakeholders were recorded .



Table 4.6 Main pros and cons of policy tools at the health care system level
(according to stakeholders)

Policy tool	Pro	Con
Reimbursement of off-label product out of economic reasons in case there is an on-label competitor (and where the off-label product is cheaper)	Budget control at MS level and sustainability of the health care system can be reached by prescribing the cheaper off-label option Medicines available for patients who might not be able to receive the product otherwise (in case the on-label product will not be reimbursed at all)	(Only) reimbursing the off-label product in a situation where an on-label product exists, is a policy tool that is strongly opposed by the representatives of pharmaceutical industry who find off-label use not the right platform to address high costs of medicines. (Only) reimbursing the off-label product in a situation where an on-label product may ultimately lead to court cases
Reimbursement of off-label product out of economic reasons in case there is no on-label competitor	In case there is no on-label alternative, the reimbursement of off-label products makes treatments available for patients who otherwise might not have been treated.	In case the off-label treatment is reimbursed and expensive this might put a pressure on the budget control at MS level and sustainability of the health care system

4.7.3 Professional and patient level

Table 4.7 summarises the pros and cons of policy options to address off-label use at the professional and patient level.

Treatment guidelines on off-label use based on available evidence

Overall, treatment guidelines were considered important and strong tools in off-label use. Stakeholders agreed that guidelines can provide guidance in the field of off-label prescriber, especially if these guidelines are disease specific or focus on an active substance group. The guidance provided is based on evidence on what treatment is generally best for patients with a specific disease /medicine and provides insights in the risk-benefit ratio of products. This can be from clinical trials but also from real world evidence and monitoring. This evidence is easier to include in guidelines than in the SmPC, which are owned by the MAHs. Yet, it was also agreed that choices for off-label use of medicinal products should remain the responsibility of the health care professional who knows what is in the best interest of an individual patient.

Awareness campaigns / patient & HCP information

With regard to patient information stakeholders in the expert meeting agreed that general (either European or national) awareness campaigns for health care professionals are of limited value, amongst others due to different needs per country. Yet, in some specific cases rising awareness has been proven to be positive (e.g. chemotherapeutical treatment of breast cancer in pregnant women). Overall, individual messages to patients were considered as much better than general patient campaigns. There was wide support that patients should be properly informed in order to be able to make a shared decision, and for patients to give informed consent. This information should be provided by healthcare professionals, but other sources such as easily accessible online or printed information should be available as well. According to the pharmacist organisation PGEU patients would be better informed in case the pharmacist knows the indication for the prescription. This would make it possible for a pharmacist to act properly in case of off-label use, e.g. to inform the patient on the



fact that the off-label use is not included in the patient information leaflet of the commercially available medicinal product.

Table 4.8 Main pros and cons of policy tools at the HCP and patient level

Policy tool	Pro	Con
Professional guidelines on off-label use based on available evidence	Easier to include new scientific evidence in guidelines compared to the SmPC (MAH is owner of SmPC), especially information other than industry-based clinical trial data Provide guidance based upon evidence on what treatment is generally best for patients with a specific disease /medicine	Choices for off-label use of medicinal products remain the responsibility of the health care professional and as such it should not be compulsory to follow the guideline ((e.g. to get reimbursement).
Awareness & information campaigns for patients and professionals	Specific population campaigns may arise awareness on off-label use Individual messages are valuable and should be accompanied by good written/digital information Individual patient information enable patients to make a informed shared decision, and give informed consent.	General awareness campaigns are too general and do not address specific populations, neither for prescribers nor patients.



5. Analysis

5.1 Introduction

The previous chapter provided a description of the results from the different data collections performed within the context of the study. That information was collected in order to be able to make a factual analysis of off-label use and practices in the EU Member States (including national legislation and case law where relevant) against the EU legal framework, and to identify particular aspects and/or therapeutic areas of off-label use that would deserve specific attention at EU level. This analysis is presented in chapter 5. The chapter starts with an analysis of the EU legal framework and the interplay with national regulations (section 5.2.2), followed by an analysis of the impact of two EU-level measures on off-label use: EU Paediatric Regulation and EU Regulation on Orphan Medicinal products on the off-label use of medicinal products (section 5.2.3). Section 5.3 combines the information of chapters 3, 4 and 5.2 when analysing a variety of policy options in the field of off-label use. Some examples of such options are the regulation of the permission to prescribe off-label, a legal framework to issue temporary recommendations for off-label use, providing incentives for pharmaceutical companies to register new indications and providing EU guidance for national guidelines on off-label use. For each of the policy options that are described the following aspects are considered:

- The content of the policy option (what does it mean?);
- The impact of the policy option on patients, health care professionals, and the health care and regulatory system;
- Consequences in terms of liability;
- The position of different stakeholders on this option;
- Interplay with and implications regarding the EU regulatory framework.

In section 5.4 the policy options are related to the drivers of off-label use as described in section 4.4. This will be done in order to see whether and how policy options can influence the forces that drive off-label use. Moreover, measures may be more important for some patient groups than others. Therefore, section 5.5 describes for each of the areas of specific interest for off-label identified in section 4.3 (such as children, the elderly and pregnant women) all information available and relevant to these areas described in sections 4.2 to 4.7 and 5.2 is summarized below, supplemented by the authors with an overall conclusion per area.

5.2 EU legislation and national frameworks

5.2.1 Marketing authorisation and medical practice

In Chapter 3 it is stated that the distinction between the regulation for the **authorisation** of medicinal products and the **use** of medicinal products in medical practice is important when studying off-label use. In short, the EU legislation on medicinal products is based on the premise of free movement of goods and to ensure public health. Additionally, the EU legislation includes as a general rule the requirement for a marketing authorisation, and only allows a limited number of exemptions under strict conditions.

Off-label use is not directly regulated in EU pharmaceutical law. As mentioned in previous sections, the EU General Court concluded that in the EU, off-label prescribing is not prohibited, or even regulated by law. In general, EU law only regulates



products and not the way products are ultimately used in medicinal practice. This also reflects the limited powers of the Union in the field of public health (Article 168) TFEU). The strict legal framework only allows medicinal products to be placed on the market if a marketing authorisation has been granted after a rigorous benefit/risk assessment for a specific indication in a well-defined population. Once a medicinal product is placed on the market physicians may prescribe the medicinal product off-label for a wide variety of conditions in any patient: there is a general expectation that the HCP would prescribe on-label, but there is the freedom of prescription.

In France, under an RTU a medicinal product is reimbursed for an off-label indication or purpose, while the pharmaceutical company collects efficacy and safety data and eventually should apply for an extension of indication. Originally, the RTU was limited to situations in which no therapeutic alternative was available. In 2014, France amended its legislation to include off-label use in case there is no medicinal product having the same active substance, the same dosage and the same dosage form licensed for the intended off-label use, so despite the availability of a medicinal product that, for instance, contains a different active substance. On the one hand, one might question whether such legislation would circumvent the need for a marketing authorisation. On the other hand, Member States hold the competence to decide on reimbursement of medicinal products and to arrange medical practice, as also addressed in chapter 3.

In chapter 3 it has been pointed out the CJEU concluded in case *Commission v Poland* that Article 5 (1) *“can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market. No such special need exists if there are already authorised medicinal products available on the national market with the same active substances, the same dosage and the same form. Furthermore, financial considerations do not lead to a special need”*.

5.2.2 Results of the Paediatric Regulation and the Orphan Medicinal Product Regulation

Paediatric Regulation

The Paediatric regulation was evaluated by the European Commission in 2013.^{jjjj} Here, we describe the results for the availability of medicines for children. For other results of the Paediatric regulation, we refer to the report of the European Commission. By the end of 2012, the EMA had agreed 600 paediatric investigation plans (PIP), 147 of which were related to new indications for patent-protected products. The other 453 were for medicines that were not yet authorised in the EU. By the end of 2012, 33 of these PIPs were completed. Since the Paediatric Regulation became into force, 31 out of 152 new centrally authorised medicines have been authorised for paediatric use. Overall, it seems that the paediatric regulation has led to an authorisation of a number of new paediatric indications and new pharmaceutical forms, routes of administration, or strengths for paediatric use. In a review Ivanovska et al concluded that, so far, diseases that only occur in children (e.g. paediatric oncology, neonatal morbidity) were less well represented in the PIPs: only a quarter was exclusively submitted for

^{jjjj}https://ec.europa.eu/health/sites/health/files/files/paediatrics/2013_com443/paediatric_report-com%282013%29443_en.pdf



such diseases. As such, they concluded that the development of medicines for paediatric populations significantly depends on the developments of medicines for the adult population. As such, the development of medicines for the paediatric population is market-oriented rather than that it focuses on unmet paediatric needs.⁶ The Commission stated in its 2013 report that, in order to gain full understanding of the impact of the legislation a ten-year period is needed. Therefore, the Commission is expected to publish a new report in 2017.

Orphan Medicinal Product Regulation

Currently, there are 1435 orphan designations.^{kkkk} An application for an orphan designation is considered a serious intention by a pharmaceutical company to develop a medicinal product for an orphan disease.⁵⁷ Yet, not all designations lead to marketing authorization. In 2011, 114 marketing applications were done, which have led to authorisation of 59 orphan medicinal products for 73 indications.⁵⁸ Oncology is the field where most applications were done. They covered about one third (35%) of all applications for orphan medicinal product; 70% of these applications were approved.⁵⁹ As such, rare cancers account for the highest number of orphan designations and marketing authorisations in the EU. The Orphan Regulation thus stimulates new medicines to be developed in areas where – without this regulation – fewer medicines would have been developed and off-label use of existing medicines might have been the only option to treat patients. MAHs may also request an orphan designation for a product that already has a marketing authorisation. This would have to be separate marketing authorisation for the orphan indication, using a different proprietary name. Orphan and ‘non-orphan’ indications may not be covered by the same marketing authorisation. Thus it is not possible to extend the existing marketing authorisation to cover the new orphan indication.^{llll} Putzeist et al studied 114 marketing applications for orphan medicinal products that received a favourable opinion by the CHMP or were withdrawn by the sponsor during the authorisation procedure (period 2000-2009). Only 13 (< 10%) were applications for extensions of indications of previously approved drugs by the EMA, 97 were applications for new orphan medicinal products (including four double applications for the same indication). This means that the Orphan Regulation mainly indirectly of importance for off-label use: new medicines are developed for areas where otherwise non-authorised products might have been used off-label.

5.3 Policy options: analysis

5.3.1 Introduction

Figure 5.1 provides a scheme on factors and policy measures having an impact on off-label prescribing. The decision to prescribe and use a medicinal product off-label is made by the prescriber in a shared decision with the patient. Many factors may influence this decision process, with obviously availability of an on-label option as one of the key aspects: if no on-label option is available, the choice can either be ‘no pharmacotherapy’ or ‘off-label prescription’.

^{kkkk} See for all designations:
<https://ec.europa.eu/health/documents/community-register/html/alforphreg.htm>; last time consulted, February 21, 2017

^{llll}

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000014.jsp&mid=WC0b01ac058061ecb9

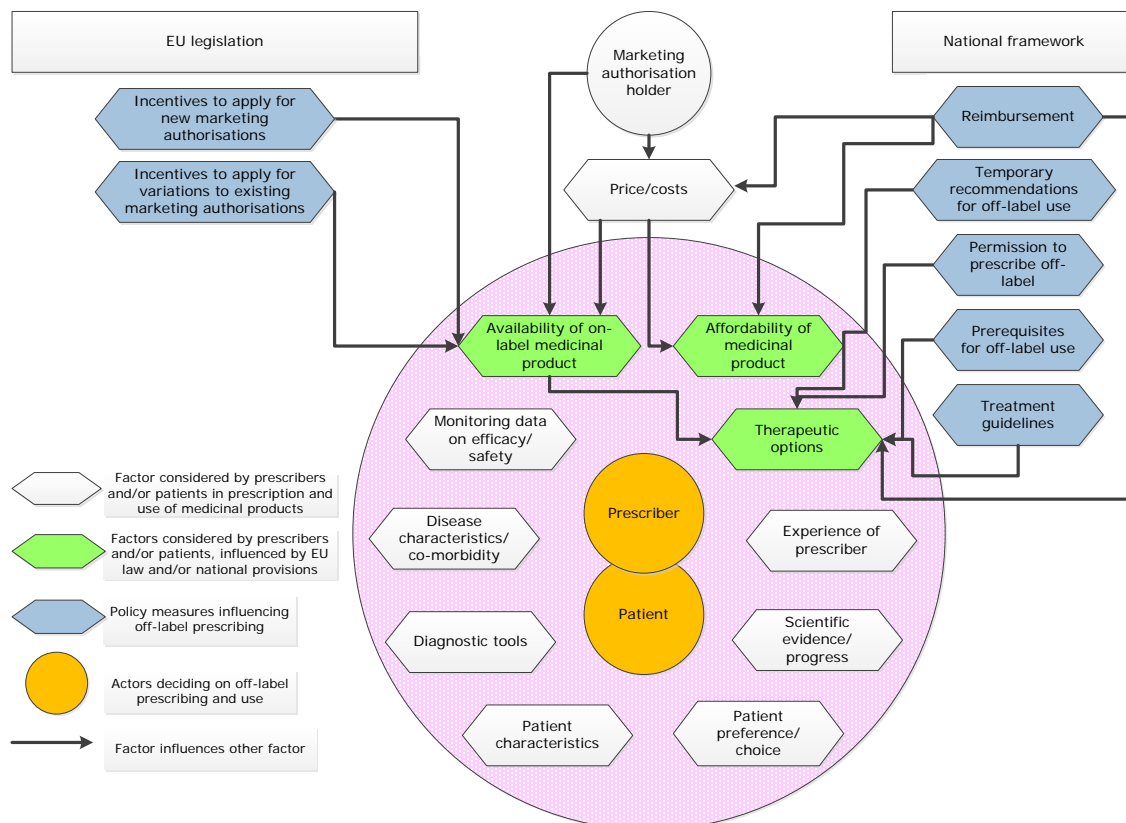


Below, ten policy options are discussed based on the findings previously described in this report (chapter 3 and sections 4.3, 4.5 and 5.2). Table 5.1 summarises per policy option information on:

- The content of the policy option (what does it mean?);
- The impact of the policy option on patients, health care professionals, and the health care and regulatory system;
- Consequences in terms of liability;
- The position of different stakeholders on this option;
- Interplay with and implications regarding the EU regulatory framework.

We analysed the policy options guided by these topics. In the text we only highlight the most important issues, mainly looking at consequences for patient safety and public health as well as legal consequences. Table 5.1 includes more detailed information. Chapter 6 will discuss how these policy options can be of use at the EU and Member State level. In this regard, it is important to note that there is no consensus about the role of the EU in the regulation of off-label use among stakeholders. Some Member States representatives and especially European –level stakeholders pleaded for a more prominent role of the EU in legislation on off-label use, while most Member States argue that off-label use should firstly be regulated at the national level.

Figure 5.1 Scheme on factors and policy measures having an impact on off-label prescribing





5.3.2 Policy options at the regulatory level

Six policy options at the regulatory level were discussed. When looking at figure 5.1, five of these options fall under the national framework:

- Regulating the permission to prescribe off-label (Permission to prescribe off-label);
- Encouraging requests for extension of indications by using new models such as RTU (Legal framework to issue temporary recommendations for off-label use);
- Use of evidence other than industry-based RCTs for MAHs to support the application of an extension of the indication; use of evidence from patient registries (Monitoring data on efficacy and safety);
- Use of evidence other than industry-based RCTs for MAHs to support the application of an extension of the indication; use of evidence from obligatory adverse event reporting (Monitoring data on efficacy and safety);
- Providing guidance at EU level for national guidelines on off-label use (Treatment guidelines);

And one falls under EU legislation:

- Providing incentives for pharmaceutical companies to register a new indication.

Permission to prescribe off-label

The systems that are in place in for example Hungary and France have a national legal framework governing off-label use. The Hungarian and French systems are examples of systems that, although different in their form, attempt to provide a national legal framework.

The Hungarian system (Table 5.1a) aims to provide permission to prescribe off-label. For both patients and prescribers this leads to access to medicinal products with an established risk-benefit analysis. This is positive with regard to patient safety and public health. Moreover, for prescribers this may lead to a stronger position with regard to liability. A downside is that the evaluation may lead to a refusal. While this might be for the benefit of the whole population, it may be disadvantageous for individual patients. The evaluation is – like the market approval – based on population effects. The off-label use in the individual case may be prohibited based on the evaluation of the average of the risk/benefit ratio. One could argue that restrictions of prescribing in the framework of the protection of public health should be acceptable. Secondly, under EU law any (regulatory) decision that could harm a (legal) person's interests should avail of an effective legal remedy.

Legal framework to issue temporary recommendations for off-label use

France has a “temporary recommendations for use (RTU)” scheme in place (Table 5.1b). The objectives of this scheme are: 1) safer off-label use of medicines as patients should be monitored through a protocol, 2) to improve the knowledge regarding efficacy and safety of off label use, and 3) to encourage the pharmaceutical companies to file an MA extension. A RTU is set up at the initiative of ANSM. ANSM informs MAH about the need of a RTU and asks him to provide all available data on the concerned indication. The RTU includes the obligation for the MAH to set up a follow up of patients based on safety and efficacy information, and real conditions of use. A legal request from pharmaceutical industry to amend the rules of the RTU was rejected. Nonetheless, according to the French stakeholders interviewed, there is reluctance of some MAHs to implement the follow-up of patients. Moreover, there is reluctance of physicians to include patients into the RTU because of the weight of the tasks linked to the reporting.

Monitoring data on efficacy and safety

Another policy option is the use of other than industry-based RCTs as evidence for MAHs to include in their application for marketing authorisation (Table 5.1c), for



example by using monitoring data on efficacy and safety. Using other evidence than industry-based RCTs can increase the knowledge on the risk-benefit balance of medicinal products and as such could be used in order to establish whether a medicine could be registered for a new diagnosis. Such data are especially useful if RCTs are hard to organise. However, evidence from other sources than RCTs is usually less solid. In order to ensure patient safety it should be clear which quality standards should apply for these other data: what requirements do these data have to meet in order to be acceptable as evidence in the marketing authorisation process. These standards could be developed at EU level. In case this information is allowed in the marketing authorisation process, liability for prescribers is the same as for on-label use of authorised products. The above arguments also hold for the use of real-world data from patient registries in the marketing authorisation process. Patient registries include real-world information on efficacy and side effects of off-label used medicines on a patient level (Table 5.1d). Personal data protection is an important issue in this regard.

Another policy option is to monitor safety by reporting of adverse events (Table 5.1e). This policy option fits in the call made in Directive 2010-84-EU (recital 17) to Member States to operate pharmacovigilance systems to collect information that are useful for the monitoring of medicinal products. This is important with regard to patient safety. Reporting adverse events could be either obligatory or voluntary. Voluntary reporting where HCPs are taught the importance of reporting combined with anonymous voluntary reporting is preferred by virtually all stakeholders. Reasons for this include the question of liability in case of reporting adverse events in an off-label situation and the fear it may give prescribers to report because of this liability. Moreover, reinforcement of obligatory reporting is expected to be hard to establish.

Providing EU guidance for national guidelines on off-label use

Guidance on how off-label use can be addressed in national treatment guidelines was an option suggested during the expert meeting with stakeholders (Table 5.1f). There were no counter-arguments given; broad consensus on this option was observed. These stakeholders stated that treatment guidelines should preferably developed in Member States. But guidance at EU level could provide a common ground for national treatment guidelines in EU Member States. Such guidance could also include information on the relation between regulations and treatment guidelines. There are no direct consequences for patient safety, only indirectly through treatment guidelines (see below).

Incentives for pharmaceutical companies to register new indications

Legislation allows an additional year of market protection for new indications developed within the first eight years of the ten-year period of marketing protection of a new medicinal product (see Article 10(1) fourth subparagraph of Directive 2001/83/EC and Article 14(11) of Regulation 726/2004). A prerequisite is that the new indication brings a significant clinical benefit in comparison with existing therapies. For patients and prescribers, it means that more authorized products with a proper risk-benefit analysis are placed in the market. This enhances patient safety. For prescribers it means a stronger position with regard to liability. At the system level, incentives can lead to better access to medicines which is beneficial for patients who are in medical need for a certain treatment and as such for public health. Stakeholders from the pharmaceutical industry argue that more incentives (than already in place) need to be part of the EU legal framework (Table 5.1g); however, all other stakeholders present at the expert meeting consider the current incentives (including the Paediatric Regulation and Orphan Drug Regulation) as sufficient.



5.3.3 Policy options at the health care system level

Reimbursement measures have direct impact on off-label prescribing (see Figure 5.1). These measures are within the remit of the individual Member States, which have as an important task to keep their health care systems sustainable. This may conflict with providing care that meets the medical needs of all individual patients as not all care can be reimbursed or delivered. With regard to off-label use there are different potential measures (Table 5.1h), for example:

- only reimbursing off-label use in case of evidence (for example resulting in inclusion in treatment guidelines);
- only reimbursing products for which there is no competitor in the market;
- allowing reimbursement of off-label use in case the off-label product is less expensive than its on-label competitor.

Especially this last option causes discussion. The Court of Justice clarified, in the court case of the *European Commission v Poland*, that the exemption to the marketing authorisation requirement in article 5 cannot be applied for financial reasons only. Stakeholders agree that medical need should be leading. It can be debated whether allowing reimbursement of off-label use in case it is less expensive than its on-label competitor is (always) against the medical need of an individual patient. Moreover, medicinal products may become available to patients who otherwise would not have access to these medicines. This view is opposed by stakeholders from the pharmaceutical industry. Also at the Member State level, reimbursement of off-label use is an issue. National case law most often targets reimbursement of off-label use. This case law mainly implies that additional requirements may apply (such as limiting reimbursement to life-threatening diseases).

5.3.4 Policy options at the HCP and patient level

HCPs and patients are the central actors when it comes to off-label use (see Figure 5.1). Many stakeholders from different backgrounds agree that treatment decisions are in the end the responsibility of the prescriber who has to inform patients so that these can give informed consent. Pharmacists also have the obligation to inform patients. Yet, in many countries the pharmacists do not know for what indication the medicine has been prescribed, which hampers them to properly inform patients when it comes to off-label use. Policy options at this level include:

- Treatment guidelines on/including off-label use
- Awareness campaigns

Treatment guidelines

In the Netherlands, off-label prescription is allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use (Table 5.1i). If protocols or standards are still under development, the physician and the pharmacist are required to consult each other about off-label use. Choices for off-label use remain the responsibility of the prescriber as guidelines usually are not compulsory. This is in line with the widely shared opinion of stakeholders that the main responsibility for a patient's treatment is with the patient's own prescriber. The evidence on which guidelines are based, provides insights in the risk-benefit ratio of products so that prescribers – and patients – can make an informed decision on the off-label use. This is positive for patient safety. The liability for prescribers does not change compared to a situation without the existence of a treatment guideline as they are still responsible for the decision to prescribe. If off-label use within treatment guidelines would be approached in a similar and harmonised manner in EU Member States, this could contribute to a harmonized positioning of off-label use in relation to EU legislation on marketing authorisation.



Awareness campaigns

Awareness campaigns for patients and HCPs can be used to inform them about what off-label use is and what it means in clinical practice (Table 5.1j). Such campaigns can be organized by different bodies, for example professional organisations, patient organisations, government and/or regulators. General campaigns for HCPs are not useful as needs for information may differ per country and per specialism. Information tailored to the needs of specific groups of HCPs is preferred. Campaigns that target the general public might not be useful either as off-label use is not relevant for most citizens. Individual messages tailored to the need of the patient provided by HCPs are preferred above general patient campaigns. In other words: information to those who need it at the moment they need it. This information should be accompanied by easily accessible online and printed information such as the UK website with information focused on off-label use in children:

<http://www.medicinesforchildren.org.uk/unlicensed-medicines>. There are no legal aspects to discuss with regard to this option.


Table 5.1a Policy option: Regulating the permission to prescribe off-label (Example: Hungary)

What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option ^{mmmm}	Interplay with and implications regarding the EU legal framework
<p>For off-label prescription of medicines physicians need to apply for permission (an application license) at a designated competent authority. This authority collects empirical evidence and, based upon this evidence, decides whether or not to grant permission.</p> <p>As a pre-requisite to apply for permission, the patient's consent is needed.</p> <p>Once permission has been provided, this will be published and no further applications by other HCPs need to be done.</p> <p>For off-label use covered by published permissions or by healthcare professionals' protocols a simplified application for permission may be submitted.</p>	<p><u>Impact on patients:</u> It increases access to treatments approved by a competent authority based on available evidence.</p> <p>It strengthens the position of patients because patients can get more evidence-based information to make an informed decision.</p> <p>It takes time to get approval which – in case of severe diseases – may have a negative impact on the patient.</p> <p><u>Impact on HCPs</u> More assurance on benefit/risk as the use is approved by a competent authority based on available evidence. However, it also implies two different systems of authorisation, which may be confusing.</p> <p>Administrative burden for HCPs to ask for permission, including a time lag before permission is granted.</p> <p><u>Impact on health care system and regulatory bodies</u> Better overview of the products prescribed off-label and the patient groups treated off-label.</p> <p>Manpower needed to perform the evaluation of the evidence and administrative burden for the competent authority to process the approval request.</p> <p>Resources needed for the competent authority and the overseeing inspectorate for reinforcement.</p>	<p>It is expected that this improves the position of the prescriber in terms of liability.</p>	<p>Off-label use can undermine the marketing authorisation process (according to some of the national regulators, EU patient organisations, EU pharmaceutical organisation).</p>	<p>One could argue that restrictions of prescribing in the framework of the protection of public health should be acceptable. Secondly, under EU law any (regulatory) decision that could harm a (legal) person's interests should avail of an effective legal remedy.</p>

^{mmmm} See Chapter 4 for details on the stakeholders and their position.



Table 5.1b Policy option Encouraging requests for extension of indications by using new models such as RTU (Example: France)

What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option	Interplay with and implications regarding the EU legal framework
<p>A new model is for example the temporary recommendations for use (RTU) in France. The competent authority informs the marketing authorisation holder (MAH) about the need of a RTU and asks the MAH to provide all available data on the concerned indication.</p> <p>A medicine covered by a RTU can be reimbursed by the national health insurance also if there is an on-label alternative.</p> <p>The prescriber has to inform the patient of the off-label use and of the potential benefits and risks attendant to the use.</p>	<p><u>Impact on patients:</u> Increased access to products for which a risk-benefit analysis is established. Patients can give informed consent based on this risk-benefit information.</p> <p><u>Impact on HCPs</u> HCPs can prescribe a product for which a risk-benefit analysis is established.</p> <p><u>Impact on health care system and regulatory bodies</u> More products enter the regulatory system and there are more products for which a risk-benefit analysis is established. It also leads to a better overview of indications for which medical products are prescribed.</p>	<p>It is expected that liability with this option is similar to that for all authorized products.</p>	<p>Off-label use can undermine the marketing authorisation process (according to some of the national regulators, EU patient organisations, EU pharmaceutical organisation). By stimulating registration of off-label indications – the ultimate goal of the RTU – this can be reduced.</p>	<p>The RTU can be considered, in accordance with the European Court of Justice court cases, to fulfil a special need, if the benefit/risk ratio of the medicinal product is presumed to be favourable.</p> <p>On one hand, some stakeholders question whether such legislation would circumvent the need for a marketing authorisation. On the other hand, Member States hold the competence to decide on reimbursement of medicinal products and to arrange medical practice.</p>


Table 5.1c: Policy option: Use of evidence other than industry-based RCTs in marketing authorisation process

What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option	Interplay with and implications regarding the EU legal framework
<p>Accepting other evidence than industry-based RCTs in the market authorisation process for registering new indications for existing products.</p> <p>This would mean that real-world evidence, collected by industry or, provided that products are no longer patent-protected, by other parties, could be included in the evidence serving as the basis on which the regulator decides whether or not to grant authorisation for an indication.</p>	<p><u>Impact on patients:</u> There is more information available on risk-benefit balance of a product and allows for application of new scientific insights especially for patients with rare diseases where RCTs are problematic due to low numbers of patients.</p> <p><u>Impact on HCPs</u> There is more information available on risk-benefit balance of a product and it allows for application of new scientific insights. This increases the scientific profile of the product and can be put in professional guidelines.</p> <p><u>Impact on health care system and regulatory bodies</u> Regulatory bodies (EMA and national bodies) have to develop standards for when other evidence is valid and of a sufficiently academic level to be included in the risk-benefit evaluation of a product. This because of the fact that the evidence is considered to be less solid compared to that from a RCT.</p> <p>Increasing the evidence of off-label used could be done by investigator driven studies (preferably RCTs). IMI-like initiatives should be encouraged for the most relevant off-label areas.</p>	<p>Similar to that for all authorized products in case this type of information is allowed in marketing authorisation process.</p>	<p>Stakeholders general see advantages of this policy option for rare diseases.</p> <p>Views are divergent (across different types of stakeholders) with respect to the question whether evidence from other sources than the industry should be included in the SmPC of a product. Another option would be to include this information in health care professional guidelines.</p>	<p>Standards for evidence derived from other sources would need to be developed by at EU level in cooperation with national regulatory bodies. That ensures that these standards are developed within the legal framework of the Europe.</p>


Table 5.1d: Policy option: Information on off-label use through patient registries / databases

What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option	Interplay with and implications regarding the EU legal framework
<p>Patient registries include information on efficacy and side effects of off-label used medicines on a patient level. Such patient registries are valuable as they enable to monitor efficacy and adverse effects of off-label use and establish whether off-label use is rational or not. Patient registries can, for example, be coordinated in academic settings</p>	<p><u>Impact on patients:</u> Patient registries provide evidence on off-label use. This enables the decision-making process in the doctor's office as more information is available for patients and prescribers.</p> <p><u>Impact on HCPs</u> There is more information available on the risk-benefit balance of a product and allows for application of new scientific insights. This increases the scientific profile, can be put in professional guidelines. This enables the decision-making process in the doctor's office as more information is available for patients and prescribers.</p> <p><u>Impact on health care system and regulatory bodies</u> Patient registries provide information on the risk-benefit balance of a product and allows for application of new scientific insights. This increases the scientific profile of the medicinal product. In case regulators want to include evidence from patient registries in the authorisation process, standards need to be formulated.</p>	<p>Similar to that for all authorized products in case this type of information is allowed in marketing authorisation process.</p>	<p>In the stakeholder meeting, stakeholders agreed that for patient registries to be helpful, some important conditions need to be met, including:</p> <ul style="list-style-type: none"> - To get the most valuable information, notifications that are valuable for databases should be anonymous and not contain patient- or practitioner identifying information as this might hamper prescribers to register information; - E-prescriptions are important and useful for this aim; - The administrative burden for health care professionals should be limited. 	<p>Standards for evidence derived from other sources would need to be developed at EU level in cooperation with national regulatory bodies. That ensures that these standards are developed within the legal framework of the Europe. Personal data legislation needs to be adhered to.</p>



Table 5.1e: Policy option: Use of evidence from obligatory adverse event reporting in the market authorization process

What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option	Interplay with and implications regarding the EU legal framework
<p>Obligatory reporting of adverse events in case of off-label use by prescribers to a designated authority.</p> <p>Many Member States already have adverse event reporting mechanisms in place.</p>	<p><u>Impact on patients:</u> An increase in the knowledge on the risk-balance benefit in case of off-label prescribing and as such it may support decisions in the doctor's office.</p> <p><u>Impact on HCPs</u> An increase in the knowledge on the risk-balance benefit in case of off-label prescribing and as such it may support decisions in the doctor's office.</p> <p>Liability in case of non-anonymous reporting may be an issue and it may prevent HCPs from reporting. Obligatory reporting implies that a doctor knows that a prescription is off-label, which he/she is not always aware of. Given these drawbacks, voluntary reporting would be an alternative (see also stakeholder opinion).</p> <p><u>Impact on health care system and regulatory bodies</u> Reinforcement would be needed in case reporting would be obligatory. Such reinforcement is hard to establish.</p>	<p>In case the treatment fails or the patient experiences adverse effects, the issue of liability arises. As long as the off-label treatment can be considered as appropriate the prescriber will not automatically be deemed liable for damages. Still, liability of doctors could be an issue in case of non-anonymous reporting as doctors may fear to be hold responsible.</p>	<p>Reporting as such is considered to be useful as there is widespread support among stakeholders that there recorded adverse drug events between medicines are lower in off-label use. However, there is clear consensus among all stakeholders in favour of a soft approach of adverse event reporting (increasing awareness and confidence that reporting is necessary and helpful) and deem as more effective compared to obligatory reporting.</p>	<p>Directive 2010-84-EU (recital 17) calls upon Member States to operate pharmacovigilance systems to collect information that is useful for the monitoring of medicinal products. This includes information on suspected adverse reactions of a medicinal product, also in case its use was off-label.</p>



Table 5.1f: Policy option: Guidance at EU-level

What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option	Interplay with and implications regarding the EU legal framework
<p>Development of a <u>general guideline</u> (and not treatment guidelines) on off-label use at the EU-level which describes the legal framework and regulation and the relation between regulation and professional guidelines.</p> <p>Such guideline could provide guidance on what elements could be included in national treatment guidelines on off-label use (e.g. informed consent, various levels of evidence, information for the patient, monitoring, patient involvement in preparing guidelines) and how guidelines could be developed. It would provide a common ground for national treatment guidelines in EU Member States.</p>	<p><u>Impact on patients:</u> Guidance may include guidance on how to inform patients on off-label use. This may improve information to patients.</p> <p>Guidance may also include information on how to involve patients in guideline development. This improves patient empowerment with regard to off-label use.</p> <p><u>Impact on HCPs</u> Provides guideline developers in Member States with guidance on what to include in guidelines and on the relation between guidelines and the regulatory framework at the EU-level. The result is guidelines that inform individual prescribers not only on the medical side of off-label use but also on regulatory aspects of off-label use.</p> <p><u>Impact on health care system and regulatory bodies</u> Common ground for treatment guidelines across EU.</p>	None	<p>Treatment/clinical guidelines are preferably made at the country level, but a common ground for the preparation of such guidelines is considered to be important. Therefore, it would be helpful if a general guideline on off label use of medicinal products would be developed at EU level, describing:</p> <ul style="list-style-type: none"> - the framework, e.g. legal framework and regulation, relation between regulation and professional guidelines - providing guidance on what elements could be included in guidelines on off-label use 	<p>A guideline could be prepared and adopted at EU level, but it should be in line with the competences and remit of all the actors involved.</p>



Table 5.1g: Policy option: Providing incentives for pharmaceutical companies to register new indications (Examples: Paediatric Regulation, Orphan Regulation, one year extension of market protection in case of new indications)

What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option	Interplay with and implications regarding the EU legal framework
<p>Market authorisation is a time and money consuming process. If a product is on the market, there may be too little incentives to register the product for another indication.</p> <p>At the EU-level three main measures have been taken to reduce barriers: the Paediatric Regulation, the Orphan Medicinal Product Regulation, and one year extension of market protection in case of new indications with a significant clinical benefit in comparison with existing therapies.</p>	<p><u>Impact on patients:</u> In case incentives lead to more authorized products, patients have increased access to products for which a risk-benefit analysis is established. This especially holds for patient groups for whom less authorized products are available such a children and patients with a rare disease.</p> <p><u>Impact on HCPs</u> In case incentives lead to more authorized products, HCPs can prescribe a medicine for which a risk-benefit analysis is established.</p> <p><u>Impact on health care system and regulatory bodies</u> More products enter the regulatory system and there are more products for which a risk-benefit analysis is established. It also leads to a better overview of the indications for which medical products are prescribed.</p> <p>R&D activities may be expanded, as was the case in the field of rare diseases.</p>	<p>Liability with this option is similar to that for all authorized products.</p>	<p>Off-label use can undermine the marketing authorisation process (according to some of the national regulators, EU patient organisations, EU pharmaceutical organisation). By stimulating registration of off-label indications, this can be reduced.</p> <p>This policy option is supported by stakeholders from the pharmaceutical industry. They want incentives to register for other indications to be part of the EU legal framework.</p> <p>Other stakeholders find that for most purposes there are enough incentives for the pharmaceutical industry to register their products. However, an exemption would be the example that – despite incentives created over the last decade – still few medicines are authorized for paediatric use (that could lead to the question whether the incentives so far are insufficient in this particular field).</p>	<p>This option should be considered in light of the results of a study that will soon be launched by the European Commission on the impact of Supplementary Protection Certificates and pharmaceutical incentives on innovation, availability and accessibility of medicinal products.</p>


Table 5.1h: Policy option: Reimbursement of off-label products

What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option	Interplay with and implications regarding the EU legal framework
<p>Reimbursement of medicines is regulated at the Member State level. They can decide whether or not to reimburse off-label use within their own law.</p> <p>Examples of reimbursement options are:</p> <ul style="list-style-type: none"> - Reimbursement only in case of sufficient evidence, for example demonstrated by the fact that the off-label use of the medicinal product is included in professional treatment guidelines; - Reimbursement only for those products where no authorised alternative is available; - Reimbursement of off-label products, also in cases where the off-label product is cheaper than the on-label product. 	<p><u>Impact on patients:</u> Reimbursement issues can put the relationship between patients and payers at stake if the payer refuses to reimburse an off-label treatment.</p> <p>Medicines might be available for patients who otherwise would not have access to certain medicines.</p> <p><u>Impact on HCPs</u> Reimbursement issues can put the relationship between HCPs and payers at stake if the payer refuses to reimburse an off-label treatment.</p> <p><u>Impact on health care system and regulatory bodies</u> Reimbursement policies provide opportunities for budget control and sustainability of the health care system; this also includes off-label use.</p> <p>Reimbursement issues may put pressure on the relationship between some national authorities and the pharmaceutical industry in case off-label use is reimbursed when the off-label product is less expensive compared to the authorized product.</p> <p>Reimbursement issues can put the relationship between patients/prescribers on the one hand and payers on the other hand at stake. Such situation can occur if the payer refuses to reimburse an off-label treatment.</p> <p>Reinforcement of requirements for reimbursement of off-label use is hard and puts an administrative burden on the health care system (payers).</p>	<p>Reimbursement measures may influence prescriber's choices.</p>	<p>All stakeholders: medical need should be leading in off-label use, not cost-related arguments.</p> <p>Stakeholders from the pharmaceutical industry: off-label use is not the right platform to address high costs of medicines.</p> <p>Regulators, reimbursement bodies: Medical need should be leading, but at a Member State level other factors should be taken into consideration as well such as budget control and sustainability of the health care system.</p>	<p>Reimbursement of medicines is regulated at the Member State level. Within the EU legal framework, member States can independently decide whether or not to reimburse off-label prescribing products.</p> <p>The CJEU clarified in the court case of the European Commission versus Poland the meaning of article 5 of Directive 2001/83: It emphasised that the exemption to the marketing authorisation requirement in article 5 (also known as named-patient use) cannot be applied for only financial considerations.</p> <p>National court cases about off-label use are mainly in the area of reimbursement. These cases indicate that additional requirements may apply, including the limitation to life-threatening or severe diseases or the absence of alternative options.</p>



Table 5.1i: Policy option: Professional treatment guidelines on off-label use (example The Netherlands)

What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option	Interplay with and implications regarding the EU legal framework
<p>Advices are based on evidence that is evaluated by their professional organisation or a designated guideline commission. This evidence can be from clinical trials but also from real world evidence and monitoring.</p> <p>In the Netherlands, Off-label prescription is allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use. If protocols or standards are still in development, the physician and the pharmacist are required to consult about off-label use.</p>	<p><u>Impact on patients:</u> Patients get access to treatments that are evaluated based on available evidence by the competent profession.</p> <p>It strengthens the position of patients because patients can get more evidence-based information to make an informed decision.</p> <p><u>Impact on HCPs</u> HCPs get guidance in what treatment is generally best for patients with a specific disease including the off-label options.</p> <p>Choices for off-label use remain the responsibility of the prescriber as guidelines usually are not compulsory.</p> <p><u>Impact on health care system and regulatory bodies</u> The evidence on which guidelines are based, provides insights in the risk-benefit ratio of products. This evidence is easier to include in guidelines than in the SmPC, which are owned by the MAHs.</p>	<p>The liability in case a product does have negative consequences for the patient, lies less with the prescriber only. However, in case there are problems, the prescriber is liable as guidelines are not compulsory.</p> <p>So far, no court cases related to this policy option have been filed.</p>	<p>All different stakeholders generally have a positive attitude towards addressing off-label use in professional guidelines.</p> <p>The participants in the brainstorm meeting agreed that choices for off-label use of medicinal products should remain the responsibility of the health care professional within the boundaries of the regulatory framework and/or professional guidelines.</p>	<p>None.</p>


Table 5.1j: Policy option: Awareness and information campaigns for patients and HCPs

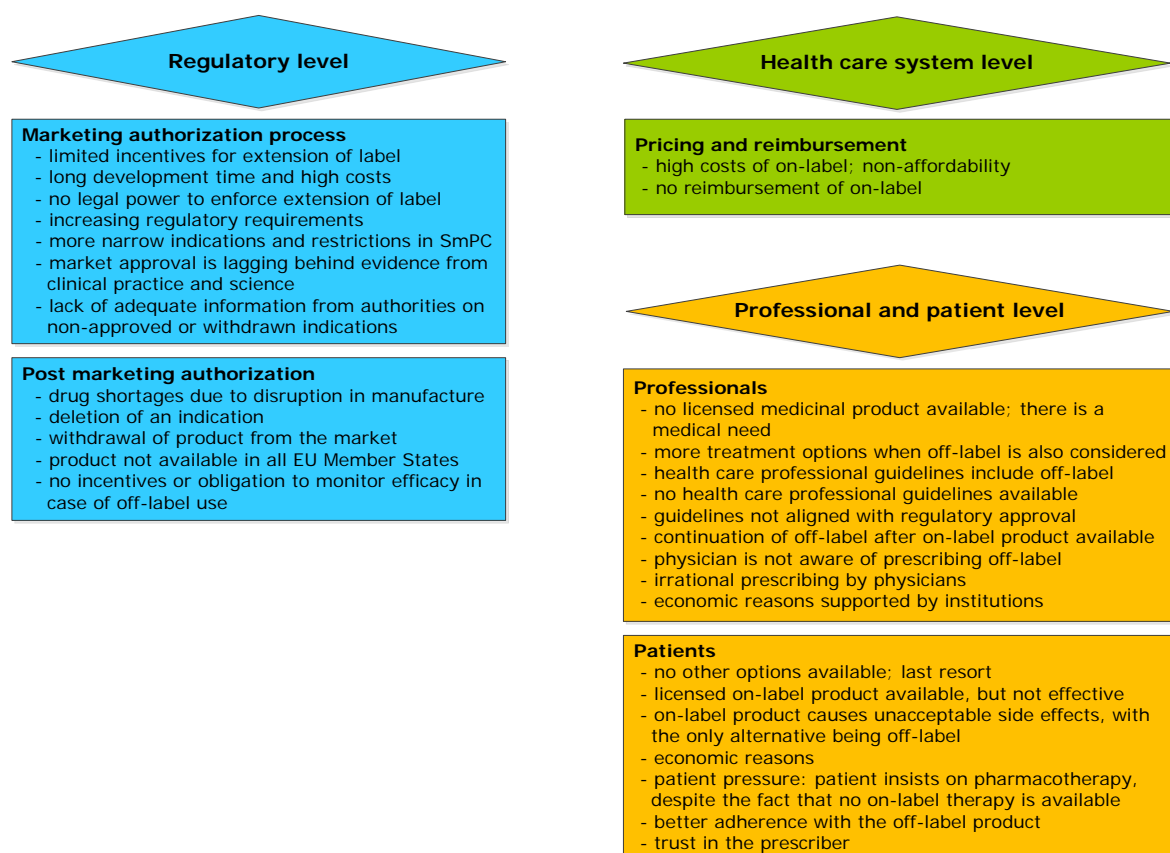
What does it mean?	Impact on patients, HCPs, health care system and regulatory bodies	Consequences in terms of liability	Position of the different stakeholders on this option	Interplay with and implications regarding the EU legal framework
<p>Awareness campaigns for patients and HCPs to inform them about what off-label use is and what it means in clinical practice.</p> <p>Campaigns can be organized by different bodies, for example professional organisations, patient organisations, government, regulators or a combination.</p> <p>Patient campaigns could be focused on all or on specific groups of patients. Campaigns can be organized in different ways, for example in mass media, by providing leaflets or by offering a website with information</p>	<p><u>Impact on patients:</u> Patient campaigns strengthen the position of patients because patients can get more evidence-based information to make an informed decision.</p> <p>If not accompanied by information by a HCP, information on off-label use might confuse patients and lead to uncertainty about their treatment.</p> <p><u>Impact on HCPs</u> Patients might be better informed on off-label use which enhances the decision-making process between prescriber and patient.</p> <p>HCPs are more aware of off-label use and what it means, for example in terms of liability</p> <p><u>Impact on health care system and regulatory bodies</u> No direct effects.</p>	<p>Risk for negative consequences is low.</p>	<p>The general opinion among all stakeholders (consensus in expert meeting) is that individual messages to patients provided by HCPs are better than general patient campaigns. This information should be accompanied by easily accessible online and printed information.</p> <p>Campaigns for HCPs are</p> <p>With regard to campaigns for HCPs, experts stated that general (European or national) awareness campaigns for health care professionals would not be of value, amongst others due to different needs per country and per specialism.</p> <p>It was felt that information should be improved with respect to communication on off-label use between hospital doctors, general practitioners and pharmacists. PGEU (pharmacists) pleas for an indication on the prescription so that they can properly inform patients.</p>	<p>None.</p>



5.4 Policy options in relation to drivers for off-label use

Figure 5.2 shows an overview of all drivers for off-label use identified in this study. In The policy options discussed in the previous section have been related to these drivers. This has been done in order to see whether and how policy options can influence the forces that drive off-label use. In the text below the policy options discussed in section 5.2 are underlined.

Figure 5.2 Overview of drivers for off-label use



5.4.1 Policy options at regulatory level

The drivers listed in figure 5.2 mainly lead to an increase of off-label use. The policy options distinguished at the regulatory level all are meant to reduce off-label use by influencing one or more drivers. Regulating permission to prescribe off-label use, for example, could counteract the first four drivers shown under *Post marketing authorisation*. Although there are advantages for all stakeholders (including possibly less problems with regard to liability of prescribers) when a permission system is in place, this also implies that two systems would co-exist regarding benefit-risk analysis on a product level. This may be confusing for prescribers and patients.

Providing incentives for pharmaceutical industry to register new indications addresses the first driver mentioned under *Marketing authorisation process* (no incentives for



extension of label). In fact, as stated by many stakeholders, this policy option is already in place for paediatrics, rare diseases and new indications for products that are still under market protection. The effect of these regulatory measures on off-label use is however unknown.

Encouraging requests for extension of indications by using new models (such as RTU in France) could overcome the lag time between evidence and market approval, as stated under *Marketing authorisation process*, and introduce obligations to monitor efficacy (see under *Post marketing authorisation*). However, this option may evoke discussion with pharmaceutical industry since the initiative to apply for extension of indication no longer lies at industry level. Moreover, liability issues and legal questions may arise.

The use of other evidence than industry-based RCTs in the marketing authorisation process could break the extensive and ever increasing requirements mentioned under *Marketing authorisation process*. However, under current legislation it may not be possible to extend the SmPC based on the benefit-risk assessment of such data. Moreover, as such the assessment of the clinical evidence may be more difficult and introduce differences compared to the current route and requirements for marketing authorisation extension. The same holds for using evidence from patient registries databases with information on evidence in the marketing authorisation process. Moreover indirectly, the gathering of evidence on efficacy and safety via other sources than RCTs could support inclusion of off-label in guidelines, increase treatment options, and lead to more rational prescribing by physicians (drivers under *Professionals*). Using evidence from obligatory adverse event reporting does not seem to address a specific driver for off-label use. Related to the marketing authorisation process, this option seems only of potential value in reducing off-label use when accompanied by obligatory reporting on efficacy and enforcing legal power to extend marketing authorisations with new indications/uses.

Guidelines at EU-level do not specifically address a driver, but could support a harmonized view on off-label use within the EU. Guidance could be given on off-label use in relation to the regulatory framework and on the way off-label use could be included in treatment guideline. This guidance should obviously not aim to address off-label use of specific products, since the medical practice per EU Member State differs considerably; differences exist, among others, regarding available medicinal products, reimbursement, price/affordability, patient needs, and medical practice. Moreover, the situation within each Member State may vary over time.

5.4.2 Policy options at health care system

Where the policy options discussed under the regulatory system all can be considered as options to reduce the necessity to prescribe off-label, reimbursement measures can (also) increase off-label use. Reimbursement of off-label products out of economic reasons may contribute to sustainability of the health care system in EU Member States, but is highly controversial. Indirectly this could influence the drivers mentioned under *Pricing and reimbursement* by putting pressure on the price of on-label products.

5.4.3 Policy options at professional and patient level

Professional guidelines on off-label use based on available evidence address many of the drivers mentioned under *Professionals*. If off-label use within these (treatment)



guidelines would be approached in a similar and harmonised manner in EU Member States, this could contribute to a harmonized positioning of off-label use in relation to EU legislation on marketing authorisation. It could also strengthen the position of patients by informing the patient and making informed consent obligatory. Moreover, it could be a chance to more efficiently monitor the efficacy and safety of off-label use and increase clinical evidence.

Awareness & information campaigns for patients and professionals affect drivers related to *Professionals* (physician is currently not always aware) as well as *Patients* (patient pressure, trust in prescriber). However, this option seems to be too general and not realistic to apply.

Conclusion

Overall, all abovementioned policy options affect most of the drivers mentioned in Figure 4.2. However, the drivers may vary per disease, per patient group, per type of medicines, and even within a certain type the drivers may vary over time. As such, it is expected that no sole policy option will be sufficient to influence all drivers. Moreover, it is not clear what the main drivers are and how they interact. This hampers a rational choice in whether or not, and what, new options to embrace.

5.5 Specificities for particular areas and/or therapeutic use

For each of the areas of specific interest identified in section 4.2, all information available and relevant to these areas described in sections 4.1 to 4.6 and 5.1 is summarized below, supplemented by the authors with an overall conclusion per area.

5.5.1 Children

Extent, drivers, pros and cons of off-label prescribing

Off-label use in children is still widespread and primarily driven by the lack of medicines authorized for children. There are various reasons reported for the low numbers of products licensed for children. First, children are a very heterogeneous group with various physiologic, mental and cognitive development stages, and with various development speeds. Together with ethical issues, this renders randomized controlled trials more difficult to perform and leads to call for the use of real world data. Moreover, diseases or disease effects may be different from adults, resulting in other medical needs. Finally, the market size is limited and current incentives may not be enough in specific cases, e.g. out-of-patent drugs⁸.

Areas of off-label use in children include infectious diseases, cardiology, dermatology, pain treatment, alimentary tract and metabolism, the respiratory system and the central nervous system. Particularly the areas of cardiology and dermatology have low percentages of authorized medicines for children compared to all medicinal products available in both categories (19%⁶⁰). The paediatric investigational plans submitted to EMA in 2007-2011, however, address both areas and may improve the situation⁸.

Current policy options

The UK and the Netherlands put emphasis on the relevance of guidelines on off-label use (see section 3.3). These two countries are dealing with the lack of medicines for children by means of a national formulary for children. These formularies provide practical information to healthcare professionals on the use of medicines in childhood



diseases, e.g. indication, dosing, side effects, contra-indications, administration. Both are regularly updated with the latest scientific evidence. This policy option could help to diminish unwanted off-label use (assuming the HCPs would be more reluctant to use medicines off-label in case they are not included in such a national standard). As such, formularies may be effective in improving rational pharmacotherapy in children.

Potential policy options

There is already an EU policy option in place: the Paediatric regulation. According to this regulation, regulatory authorities must take care that any information available for children will be assessed and adopted in the SmPC as appropriate, e.g. kinetic data. One could argue whether this encourages off-label use for indications not approved in children. On the other hand, it is important to provide all available information in order to support health care professionals in making a rational choice to prescribe off-label.

The Paediatric regulation is effective for almost 10 years now. It seems however too early to evaluate whether this regulation diminished off-label use: after evidence in children becomes available, it needs to be assessed and approved based on a positive benefit-risk balance, incorporated in the SmPC, and taken up as new practice by health care professionals when prescribing. To date, the effects of the Regulation seem to be limited, but the evaluation of the regulation planned in 2017 must be awaited before any definite conclusions on effectiveness can be drawn.

Overall conclusion

Off-label use remains an important public health issue for children. The current EU policy option, the Paediatric Regulation, awaits evaluation. On a national level, rational pharmacotherapy, including off-label use if needed, may be supported by a formulary for children.

5.5.2 Rare diseases

Extent, drivers, pros and cons of off-label prescribing

Off-label use in rare diseases is widespread and primarily driven by the lack of authorized medicines for these specific indications. One of the reasons for the lack of medicines is the large amount of diseases that falls under the definition of orphan disease (at least 6000; www.orpha.net). In addition, the small number of patients per disease hampers the conduct of clinical trials. Moreover, the cost of the clinical development process to demonstrate efficacy and safety of a new indication might not outweigh the possible financial return⁵. An exception here is the area of oncology where there is a concentration of approved orphan products⁶¹. It should be noted that orphan medicines drugs are mainly new molecules rather than existing products that are registered for a new indication.

Regulatory framework

To increase the number of registered medicines for rare diseases, the EU Orphan Regulation 141/2000/EC became effective in 2000. This EU regulation boosted research in the area.

Potential policy options

There was a call from some stakeholders for the use of real world evidence data (e.g. from patient registries, surveillance systems; see chapter 4). To date, there is only little structured data collection of real world data in the field of off-label use for rare diseases, neither in the EU nor in the individual Member States.



Overall conclusion

Off-label use remains an important public health issue for people affected by rare diseases. The current EU policy option, the Orphan Regulation, has boosted the number of medicinal products for rare diseases, but the very/ultra-rare diseases need special attention. The option of using real world evidence can be considered as a helpful option to support this as, due to the low number of patients, RCTs are difficult to establish.

5.5.3 Pregnant women

Extent, drivers, pros and cons of off-label prescribing

The extent of off-label use in pregnancy is largely unknown. Only one literature study was found, reporting off-label use in 74% of all prescriptions in pregnant women (45% for contra-indication and 25% for indication). Indeed, off-label use is expected to occur frequently in this group, primarily driven by the fact that no other options are available than to prescribe off-label.

Current policy options

No specific policy options to reduce off-label use in pregnant women are in place. However, post marketing surveillance of medicines in this group is common practice in the EU (E.g. via members of ENTIS; <https://www.entis-org.eu>).

Potential policy options

Stakeholders consider the use of real world evidence data (e.g. from patient registries, surveillance systems) in order to support (extension of) marketing authorisations as possible policy option.

Overall conclusion

The option of using real world evidence can be considered as a helpful option in making (revised) benefit-risk assessments of off-label use of medicines in pregnant women possible.

5.5.4 Elderly

Extent, drivers, pros and cons of off-label prescribing

The extent of off-label use in the elderly is largely unknown and only investigated in cardiac disease, asthma/COPD and dementia/Alzheimer. One could argue that medicinal products authorized for adults and used in the elderly is in principle not off-label (unless the SmPC mentions upper age ranges, special warnings or other restrictions for use in the elderly, or the product is used outside the terms of its license). However, the benefit-risk ratio assessed during marketing authorisation may not be applicable to elderly (see below).

Current policy options

There is no legislation in place specifically stimulating the development of medicinal products for the elderly. However, already at least since 1994 there are regulatory guidelines stimulating the inclusion of elderly in clinical studies for marketing authorisation (ICH guideline. Topic E7, 1994). Moreover, since 2011, the EMA established the Geriatric Expert Group dealing with issues related to the elderly (source: website EMA). This has resulted in more attention to gathering (post marketing) information on clinical efficacy and safety in elderly⁶². Still, clinical trials



frequently exclude elderly due to multi-morbidity⁶³. The benefit-risk ratio assessed during marketing authorisation may therefore not be applicable to elderly. In addition, guidelines may include age-specific recommendations.

Potential policy options

Stakeholders consider the use of real world evidence data (e.g. from patient registries, surveillance systems) in order to support (extension of) marketing authorisations as possible policy option.

Overall conclusion

Elderly form a grey area when talking about off-label use: formally, most medicines are not used off-label, but it is well known that the efficacy and safety of medicines are hardly investigated in elder, multimorbid patients. The lack of clinical data obtained in elderly is (still) a matter of concern. The option of using real world evidence can be considered as a helpful option in making benefit-risk assessment of medicines used in the elderly possible.

5.5.5 Oncology and haematology

Extent, drivers, pros and cons of off-label prescribing

In oncology, the extent of off-label use in children is reported in literature to be 15% (including haematology) up to 43%. In adults, percentages of 10-76% are found, depending on the type of cancer. It is not clear whether there is a main driver for this. Most obvious drivers would be on a patient level (no other options available-last resort; on-label product not effective and/or unacceptable side effects) and health care professional level (treatment guidelines; no other options available). But also drivers from the marketing authorisation process (narrow indications in the SmPC; extensive requirements for marketing authorisation) and the health care system (non-affordability of on-label medicines) could be applicable.

Current policy options

The UK and the Netherlands put emphasis on the relevance of guidelines on off-label use (see section 3.3).

Potential policy options

In oncology, indication-driven trials with combinations of medicines are preferred above active substance driven trials (in order to keep up with scientific progress). This would need a change in marketing authorisation requirements prescribed in clinical guidelines. Moreover, the trend towards more personalised medicine, especially in oncology, calls for the use of real world evidence data (e.g. from patient registries, surveillance systems).

Overall conclusion

Off-label use in oncology, including haematology, is widespread. The use of real world evidence data, a change in marketing authorisation requirements (in EMA clinical guidelines), and national (treatment) guidelines addressing off-label use, to keep up with scientific progress, may be considered as possible policy options.



5.5.6 Psychiatry

Extent, drivers, pros and cons of off-label prescribing

Off-label use in psychiatry is widespread, especially the use of antipsychotics and mood stabilizers. In literature, the reported prevalence is 25-69% of the psychiatric prescriptions to children and 79-86% of all children treated for psychiatric illness. The percentages for adults are 30-48% of the prescriptions and 29-66% of the patients. In addition, 65-94% of psychiatrists prescribe off-label. The difficulty of managing aggression and other challenging behaviour by other means than pharmacotherapy seems to be one of the drivers.

Current policy options

There are no specific policy options in place to address off-label use in psychiatry (other than initiatives aiming at reducing antipsychotic use and promote rational prescribing).

Potential policy options

No options specifically for psychiatric medicines were mentioned.

Overall conclusion

Numerous studies show that off-label use in psychiatry is widespread (see above paragraph on extent of off-label use). The literature does not provide information on drivers for this use.



6. Summary of results and conclusion

6.1 Extent and areas of off-label use in EU Member States

6.1.1 Prevalence

Prevalence figures obtained from literature are generally high, with a majority of studies reporting levels of 20% or higher for the use of off-label medication and more than 55% when looking at the percentage of doctors prescribing off-label. However, the reported figures differ considerably between and within countries. There are several reasons for this:

1. Various definitions of off-label use were applied in the studies; sometimes the investigators only refer to off-label use by indication, but in other papers also other aspects described in the SmPC were considered, such as dosing advice, target population/age, contra-indication, special warnings and administration route.
2. The prevalence figures are either expressed as percentage of the total number of prescriptions or the total number of patients or the total number of medicinal products. Based on these differences in numerator, figures cannot be compared as such.
3. The data sources differed per study. Within hospitals the investigators mostly gathered data by filling specifically designed datasheets or by reviewing medical records. These data were obtained from a variety of departments. Outside hospitals, the most frequent sources used are prescription databases, health insurance databases, pharmacy dispensing data and general practice medical records.
4. Also the time span of the data differed, with recordings of one day up to data gathered during several years. This may influence the accuracy and precision of the results. Moreover, it may matter whether point or period prevalences were reported.
5. Amongst children, the prevalence may differ per age group. Since different age groups were investigated in all paediatric studies, this may also be a cause of observed differences between studies.
6. Finally, studies were sometimes confined to a specific group of medicinal products, e.g. anti-infectives in children, intravenous immunoglobulins in adults, oncological medicines in adults. This will result in different figures compared to studies taking into consideration all therapeutic groups. This is especially true for the data shown for adults, with only two studies dedicated to a broad range of medicinal products.

6.1.2 Therapeutic areas

The literature data reveal that off-label use stretches along a wide variety of areas, with special emphasis for children on cardiovascular diseases (e.g. the use of anti-hypertensives), infectious disease (e.g. anti-bacterial agents), central nervous system (e.g. analgesic agents, psychiatry medication), respiratory system (e.g. asthma medicines), and alimentary tract and metabolism drugs (e.g. reflux medicines). For adults, the most frequently investigated areas are oncology, rheumatology, immunology, and psychiatry. The results of the interviews confirm this broad picture. In view of the differences in study designs (see above), it cannot be assessed what exactly the therapeutic areas are with the highest levels of off-label use.



Off-label prescribing in children is mostly due to the absence of approved (age appropriate) medicines for children. This obviously is not confined to specific therapeutic areas, but a general issue. The EU Paediatric Regulation, in force since January 2007, is meant to improve this situation. Another often mentioned area concerns rare diseases, for adults as well as children. The number of rare diseases is estimated to be at least 6000 (http://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN). The EU Regulation on orphan medicinal products boosted the development of orphan medicinal products, but many diseases are not yet served and represent an unmet medical need.

6.1.3 Specific patient groups

Within hospitals neonates (premature as well as full term) are the most widely investigated group of children, especially the group submitted to an intensive care unit. Indeed, this group has been identified already many years ago as deserving specific attention. The literature data show that also in the years after the Paediatric Regulation came into force, prevalence figures for off-label use remain high (e.g. 53% in 2015). It is however not known whether this differs per country.

Elderly are mentioned by the interviewees as possible group subject to off-label use. However, opinions differ, partly because elder age is seldom mentioned as restriction in the SmPC. In this respect, elderly form a grey area when talking about off-label use: formally most medicines are not used off-label as the SmPC does not provide restrictions on use in the elderly. However, the elderly often have more than one disease and their pharmacodynamics and pharmacokinetics may have changed compared with people of younger age. Multimorbidity and the aging process may affect the efficacy and safety of medicines; the outcome of the clinical studies performed for the marketing authorisation of a product may not be applicable to the elderly.

Only one study was dedicated to pregnancy, showing 74% off-label prescriptions. Due to the fact that pregnancy is often mentioned as contra-indication, this is not surprising. However, remarkably in 25% of all prescriptions in this study the off-label aspect concerned the indication.

6.2 Drivers of off-label use

The literature study and interviews conducted for this report on the drivers of off-label use provided a rich and relatively consistent view from a regulatory/health system level and from the health care professional/patient level point of view.

From a regulatory/health system level perspective, an important driver mentioned both in the literature and in the interviews was the market authorisation process. For already authorised products, there is limited drive to extend the marketing authorisation, especially for products out of patent. Also new marketing authorisation applications to fulfil a medical need, are lagging behind. The reasons for this differed slightly among the findings in literature and the interviews. A lack of incentives was mentioned as an important factor in the literature, while the duration and high costs of the authorisation procedure was mainly seen as a factor from the interviews. Another frequently mentioned driver was pricing and reimbursement issues. These issues were found across all levels (regulatory, healthcare system, professional, patient). A substantial number of interviewees mentioned that financial considerations are driving off-label prescribing, in case there is an "off-label" product that is cheaper than the



authorized product(s). In a limited number of countries off-label use of medicines is not reimbursed unless they are mentioned in health care professional guidelines.

Presence of health care professional guidelines is another frequently mentioned driver at the regulatory/health system level. Furthermore, increasing the treatment options was seen as a very important driver at both a health care professional level and the patient level. Furthermore, lack of effectiveness of other products was a driver to switch to off-label medicines for health care professionals, while safety and adherence were drivers mostly mentioned from a patient level point of view.

The results of the three case studies clearly show that it is usually a combination of drivers that influence off-label prescribing. In addition, the driver may differ in time as illustrated in the Avastin® versus Lucentis® example. The driver for off-label use of Avastin® changed in time from unavailability of an alternative to better efficacy of the unregistered medicine compared to the registered one, and then to the product with lowest costs.

This analysis of the drivers shows that off-label use of medicines is driven by many factors. These drivers vary per type of medicines and even within a certain type the drivers may vary over time. This should be taken into account when discussing the causes of off-label use for various types of medicines. A frequently mentioned driver was the marketing authorisation system. Based on the information collected in this study it can be argued that policy options affecting the marketing authorisation system could effect of off-label use although it is not clear how large this effect is.

6.3 National frameworks

The way Member States are dealing with off-label use, is not harmonized. In some countries, special provisions about off-label use are included in the national law, while other countries have good practice guidelines/professional recommendations, or steer by reimbursement decisions, or have no policy tools in place at all. In EU Member States without policy tools, the dominant view is that off-label use is an issue to be dealt with at the level of the prescriber rather than at the regulatory or healthcare system level. EU Member States with policy tools in place have incorporated these at different levels:

1. legal frameworks to issue temporary recommendations for use and permission to prescribe (e.g. a system where prescribers or their organisations have to ask for permission to use a product off-label);
2. regulating reimbursement (e.g. allow for reimbursement of off-label use if other (on-label/authorised) alternatives exist);
3. providing general guidance to HCPs (e.g. a prescribing hierarchy in which off-label is included);
4. making professional treatment standards leading (e.g. off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use)
5. focusing on the patient (e.g. the necessity to give informed consent for off-label use).

According to legal experts, in all EU Member States the competencies of healthcare professionals are laid down in either public professional legislation concerning the practicing of healthcare professions or in laws about the treatment contract between healthcare professionals and/or institutions and their patients. These national legislations contain provisions about the obligation of any healthcare professional to treat his patients as good as possible and only after patient's consent based upon full



information about possible benefits and risks, alternative treatments and predictions of what will happen if the patient decides against a treatment.

6.4 Pros and cons of off-label use

The pros and cons of off-label prescribing felt by stakeholders were generally in line with the drivers. Economic advantages and increased access to medicines otherwise not available were mentioned as important pros for off-label prescribing from a health care and regulatory system level. Some interviewees even mentioned that off-label use was an advantage for the health care system as it would improve outcomes (e.g. in case of drug shortages). However, it was generally felt that off-label use should be better monitored, information shared and guidelines developed. From a health care professional level and patient level more treatment options and earlier access to treatment are important pros for off-label use of medicines. Safety issues, adverse events and the unknown risk/benefit ratio are frequently mentioned as a disadvantage of off-label prescribing. Responsibility and liability were mentioned as main disadvantages at the regulatory/health system level. Evidence on how the medicine is used in practice is therefore important. There were divergent opinions whether off-label use should be more regulated or not. In countries with stricter regulation off-label prescribing might be more difficult, e.g. the medicines are not reimbursed or there is no negotiation about the price.

6.5 Case law

The European Court of Justice primarily confirmed that off-label use as such is not regulated by EU law and EU law does not prohibit physicians to apply medicinal products off-label. In various other cases, the European Court of Justice reflected on the marketing authorisation system as established in the EU legislation and the powers of the of the European Commission in regulating medicinal products. Such court cases are distantly of interest to off-label use. Important court cases are, among others, *Laboratoires CTRS v European Commission*, *European Commission v Republic of Poland*, *Novartis Pharma v. Apozyt*, *Novo Nordisk*. National court cases about off-label use relate to a large extend to reimbursement. These cases indicate that additional requirements may apply, including the limitation to life-threatening or severe conditions and the absence of alternative treatment options. Other national court cases concern the (professional) liability prescribing or dispensing medicinal products off-label.

6.6 Policy options

Chapter 5 provided an analysis of various policy options. Part of these options is relevant at the EU-level, other at the Member State level. In this last section we discuss what policy options can be used by EU and its Member States to address off-label use. Also, options at the level of the HCP-patient relationship will be discussed.

6.6.1 Policy options on a regulatory level

Incentives for pharmaceutical companies to register new indications and modalities

One option is creating/enhancing incentives for pharmaceutical companies to register new indications and modalities for existing products, as has been done with the



Paediatric Regulation, the Orphan Medicinal Product Regulation and the one-year extra market protection option in cases where there are new indications for products still under market protection. In this way it is attempted to have more indications registered and to avoid that the regulatory system is undermined. It leads to authorized products for which a proper benefit-risk analysis has been performed for more indications and a stronger position for prescribers with regard liability. Also, it may lead to more R&D activities by pharmaceutical companies. Stakeholders from the pharmaceutical industry are positive and argue that such additional incentives need to be part of the EU legal framework. Any new/additional incentives should take into account the revenues and progress of the incentives already in place.

Other evidence than that from industry-based RCTs

Another option at the EU-level is to explore possibilities to include other evidence than that from industry-based RCTs for marketing authorization of off-label indications and modalities and the conditions under which this would be possible. Real-world evidence from monitoring patient cohorts, data from routine patient registries and from (voluntary) adverse event reporting are examples of other data sources. This option is especially useful for those situations where RCTs are hard to organize, for example due to a low number of patients. However, evidence other than RCTs is usually less solid. When exploring possibilities to include other types of evidence, it should be made clear which standards are needed for such data to be included in the application for a market authorisation.

Important conditions for patient registries include personal data protection (no patient or practitioner identifying information) and limited administrative burden for HCPs. Another source for evidence is reporting of adverse events. According to stakeholders this reporting should preferably be anonymous and not obligatory; physicians should be able to report such adverse events without fear for potential legal consequences when they need to specify that the medicinal product was prescribed off-label.

Providing EU guidance for national guidelines on off-label use

A next policy option is providing guidance for Member States on off-label use for example by developing a general guideline on off-label use that provides guidance for the development of national guidelines (for example on what elements could be included in treatment guidelines in case of off-label use). This would also provide a common ground for national treatment guidelines which should preferably be developed in Member States as every country has its own context.

6.6.2 Policy options on a healthcare system level

Permission for prescribing off-label use / temporary recommendation for use

Off-label use is outside the legal framework in the EU and in many Member States. This might undermine the heavily regulated marketing authorisation process where quality, efficacy and safety of medicinal products are leading in granting permission for market authorisation. Hungary and France are examples of countries that, although different in their choices, both attempt to connect the marketing authorisation process to the prescription of medicinal products in medical practice. Hungary requests prescribers to apply for permission to prescribe off-label with the competent authority. As such the evidence of efficacy and safety is evaluated by a national competent body and the position for prescribers with regard to liability is stronger. France uses a temporary recommendations scheme (RTU). The objectives of the RTU are to make off-label use safer as patients should be monitored through a protocol, to improve knowledge regarding efficacy and safety of off label use, and to



encourage the pharmaceutical companies to file for a marketing authorisation extension.

Reimbursement measures

Reimbursement measures are within the remit of the individual Member States. There are different options, for example:

- only reimbursing off-label use in case of evidence (for example shown by including in treatment guidelines);
- only reimbursing products for which there is no authorised alternative in the market;
- allowing reimbursement of off-label use in case of authorised alternative (2 cases: same active substance, same strength and same form, or not).

Reimbursement measures are debated, especially by the pharmaceutical industry in case off-label prescribing is reimbursed while an on-label (and sometimes more expensive) treatment is available. The Court of Justice clarified, in the court case of the European Commission versus Poland, that the exemption to the marketing authorisation requirement in article 5 cannot be applied for financial reasons only.

6.6.3 Policy options on the HCP-patient level

A dominant view among a majority of the countries is that off-label use, first and foremost, is an issue to be dealt with at the level of the prescriber-patient relationship rather than at the regulatory or healthcare system level. Options that focus more directly on the HCPs and patients and are not necessarily to be dealt with at the regulatory or health system level. These include the development of treatment guidelines by professional bodies. These ensure HCPs receive guidance in what treatment is generally best for patients with a specific disease including the off-label options. As such, patients get access to treatments that are evaluated based on available evidence by the competent profession. Stakeholders generally have a positive attitude towards addressing off-label use in treatment guidelines as long as following guidelines is not compulsory. Another option refers to awareness campaigns for patients and HCPs to inform them about off-label use. With regard to this last option it should be noted that stakeholders generally are hesitant about its value and prefer individual messages to patients provided by HCPs accompanied by easily accessible online and printed information.



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List of abbreviations

AMD	wet Age-related Macular Degeneration
EC	European Commission
EAAMS	European Alliance for Access to Safe Medicines
EAHP	European Association of Hospital Pharmacists
EFPIA	European Federation of Pharmaceutical Industries and Association
EHA	European Haematology Association
EMA	European Medicines Agency
EU	European Union
EUCOPE	European Confederation of Pharmaceutical Entrepreneurs
EURORDIS	Rare Diseases Europe
HCP	Healthcare professional
IAPO	International Alliance of Patients' Organisations
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
PGEU	Pharmaceutical Group of the European Union
PUMA	Paediatric-Use Marketing Authorisations
RCT	Randomized Controlled Trial
RTU	Temporary recommendations for use
SmPC	Summary of Product Characteristics



Annex A Questionnaire for telephone interviews

Questionnaire for interviews with EU Member State representatives and stakeholders

Introduction:

NIVEL (Netherlands institute for health services research), RIVM (National Institute for Public Health and the Environment) and EPHA (European Public Health Alliance) are conducting a study for the European Commission on off-label use of medicinal products in the European Union. The general objective of this study is to provide the EC with a clear overview of existing and foreseen practices of off-label use across Member States and a factual analysis of all parties' positions towards the existing measures and possible future tools to regulate off-label medicine use. Hereto we are conducting an extensive literature study and complement this by interviewing relevant stakeholders. In this interview we will be asking you about existing and foreseen policy measures or tools, the extent of off-label use as well as drivers of off-label use and your view on the pros and cons of off-label use. We use a structured questionnaire for this interview and will follow this closely. You will be given room at the end of the interview to add information on topics that you missed during the interview. With your permission we would like to record the interview. This recording will only be used for the purpose of this project and will be destroyed afterwards.

Section 1: Background information

We would like to start by asking you some background information. What is your:

Organisation	
Department	
Position in the organisation	
Educational and professional background	
Relation/expertise to the subject of off-label use	

Section 2: Off-label use: existing measures and policy tools

1. Can you describe and provide us with the existing measures or policy tools to handle off-label use at European level? Are these measures and tools implemented or only available on paper?



2. What is your opinion on these existing measures or tools with regard to sufficiency and suitability? (i.e. how adequate and appropriate are they in regulating off-label use?)



3. Are you aware of any new measures or policy tools to address off-label use that are currently being developed/considered at European level? If yes, can you describe (and if possible provide) these new measures or tools?
4. Are off-label safety and/or efficacy monitored on a European level? Are there any European databases to monitor this? Are adverse drug reactions linked to off-label use (i.e. is it known when an adverse drug reaction is the result of off-label use)?

Section 3: Extent and practices of off-label use

We would now like to ask you some questions about the extent and practices of off-label use.

5. Are there any figures available on the extent of off-label use at European level? Where can we find these figures / can you provide us with these figures?
6. Are you familiar with studies on off-label prescribing at European level? If yes, can you provide us with these studies, or tell us where we can find these studies?
7. How do you perceive the extent and practice of off-label use, with regard to:
 - a) Children
 - b) Rare diseases
 - c) Elderly
 - d) Pregnant women
 - e) Therapeutic areas (e.g. oncology, psychiatry)
8. Are there any other particular areas or specific patient groups in which off-label use occurs, besides the before mentioned areas?
9. In your opinion, what areas need special attention in existing regulation? And why?

Section 4: Drivers of off-label use

10. What are the major drivers for off-label use? Can you motivate your answer?
 - a) regarding the healthcare system
Motivation for each mentioned driver:
 - b) regarding professional drivers
Motivation for each mentioned driver:
 - c) regarding patient drivers
Motivation for each mentioned driver:



Section 5: Off-label use: pros and cons

We are interested in your opinion on the advantages and disadvantages of off-label use. Similar to the previous questions, we distinguish three levels: healthcare system, professional and patient level.

11. What are advantages of off-label use? Can you motivate your answers?

a) at the healthcare system level

Motivation for each mentioned advantage:

b) at the professional level

Motivation for each mentioned advantage:

c) at the patient level

Motivation for each mentioned advantage:

12. What are disadvantages of off-label use? Can you motivate your answers?

a) at the healthcare system level

Motivation for each mentioned disadvantage:

b) at the professional level

Motivation for each mentioned disadvantage:

c) at the patient level

Motivation for each mentioned disadvantage:

Section 6: Policy tools and/or measures - what is needed

13. In your opinion, what is needed with regard to policy measures or tools, to further address the issue of off-label use at a national level?

14. In your opinion, what is needed with regard to policy measures or tools, to further address the issue of off-label use at European level?

Section 7: Court cases

15. Do you know of any court cases on off-label prescribing at European level? If yes, can you provide us with an analysis of the court cases, or tell us where to find this information? (e.g. website/experts)

16. Finally, do you have any additional information that you would like to share with us that has not come up during the interview?



Annex B Overview of Member State representatives and stakeholders who contributed

Table B.1 Representatives of Member States and stakeholders participating in the interviews

	Type of stakeholder	Remarks
Member States		
Austria	Agency (regulatory)	
Belgium	Agency (regulatory)	
Bulgaria	Medical doctor	suggested by EU patient organisation
Czech Republic	Medical doctor	suggested by regulatory officer
Denmark	Agency (regulatory)	
Estonia	Ministry of health (regulatory)	
Finland	Medical doctor	suggested by regulatory officer
France	Ministry of Social Affairs and Health (regulatory)	
	Agency (regulatory)	written response, combined answer five persons
Germany	Agency (regulatory)	written response
Greece	Off-label expert researcher (health policy/economics)	suggested by country contact
Hungary	Ministry of Social Affairs and Health (2x; regulatory), National Health Insurance Fund (OEP; reimbursement)	three interviews
Ireland	Agency (regulatory)	written response
Italy	Agency (regulatory)	written response
Lithuania	Ministry of Health (reimbursement)	
Malta	Independent expert	
Netherlands	Ministry of Health (regulatory and reimbursement)	group interview (3 persons)
Portugal	Agency (regulatory)	
Slovenia	Agency (regulatory and reimbursement)	
Spain	Agency (regulatory)	written response
Sweden	Dental and Pharmaceutical Benefits Agency (TLV), Medical products Agency (regulatory)	two interviews
United Kingdom	Public Health England; Department of Health, Agency (regulatory)	two interviews
EU-level stakeholders		
European Alliance for Access to Safe Medicines (EAAMS)	Industry and patient partners	
European Association of Hospital Pharmacists (EAHP)	Professional	
European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)	Industry	
European Federation of Pharmaceutical Industries and Associations (EFPIA)	Industry	One interview, one written response
European Haematology Association (EHA)	Professional	
European Medicines Agency (EMA)	Regulatory	group interview (8 persons)
EURORDIS, Rare Diseases Europe	Patient	
International Alliance of Patients'	Patient	



OFF-LABEL

Organisations (IAPO)		
Irish Premature Babies	Patient	
European Union of Medical Specialists (UEMS)	Professional	Two separate responses
Pharmaceutical Group of the European Union (PGEU)	Professional	

Table B.2 Participants in the expert meeting

Representatives from Member States	Representatives from stakeholders
Belgium (2)	EAHP (European Association of Hospital Pharmacists)
Denmark	EFPIA (2)
Hungary (2)	EMA
Italy	EUCOPE
Netherlands	EURORDIS
Portugal	Irish Premature Babies
Spain	NHS European office
United Kingdom	PGEU



Annex C Analysis of court casesⁿⁿⁿⁿ

Court of Justice of the European Union

Case T-13/99 Pfizer Animal Health v Council – Judgment of the Court of 11 September 2002

Issue(s) at stake

The present case relates to the precautionary principle, as well as the conflict between the interest of public health and economic interests, in which Pfizer Animal Health SA appealed at the General Court to a Council Regulation.

Factual background

Pfizer Animal Health SA ("Pfizer") marketed the antibiotic virginiamycin which was authorised as a feed additive for poultry, pigs, and eventually other species. In reliance of the safeguard clause in the relevant EU legislation, Denmark decided to ban the use of virginiamycin in feeding stuff. The basis of this ban was a report suggesting that the use of this antibiotic could cause resistance to some antibiotics, used in human healthcare to treat human infections. Moreover, there were indications that a specific bacteria could transfer from animals to human beings. At that time the so-called streptogramins (such as virginiamycin) were not used in Danish healthcare. There was, therefore, no acute threat to public health.

The issue was discussed in various scientific and regulatory bodies, leading to the adoption of a Council Regulation that contained a provision about the deletion of virginiamycin in Annex B to Directive 70/524/EEC and thus leading to the revocation of Pfizer's authorisation. Pfizer appealed the Council Regulation before the General Court. It claimed primarily that the regulation should be annulled in its entirety or as regards virginiamycin.^{oooo} The Council contended that the Court should dismiss the action as manifestly inadmissible or as unfounded.^{pppp} Some trade associations supported Pfizer; the Commission, Denmark, Sweden, Finland and the UK supported the Council.^{qqqq}

Arguments of the parties

To begin with, the arguments in respect of admissibility of the case are not relevant for this off-label report and are therefore not discussed. All parties agree that at the time when the regulation was adopted, neither the reality, nor the seriousness of the risk had been scientifically proven. It was against that background that the Commission relied on the precautionary principle as justification for adopting the regulation.^{rrrr} However, the parties do not agree on either the interpretation of that principle or whether Union institutions correctly applied that principle in the present case.^{ssss}

Pfizer c.a. take the view that the Union may not take preventive measures until a scientific risk assessment has been carried out. The outcome of this assessment must

ⁿⁿⁿⁿ An overview of court cases is available upon request from the authors

^{oooo} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 69.

^{pppp} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 70.

^{qqqq} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 71 and 72.

^{rrrr} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 113.

^{ssss} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 116.



be that the risk is not too remote: it should be probable.^{tttt} Furthermore, Pfizer submits that the fact that a measure is taken under the precautionary principle does not reverse the burden of proof.^{uuuu} The Council's opinion is that, when faced with new scientific evidence that the use of an additive poses a hazard to public health and that the hazard has reached alarming proportions since the additive was first authorised, the Community institutions are fully entitled to require the manufacturer in question to demonstrate that its product continues not to represent a risk to human health.^{vvvv}

Under the precautionary principle, the Community institutions are entitled, in the interests of human health to adopt, on the basis of as yet incomplete scientific knowledge, protective measures which may seriously harm legally protected positions, and they enjoy a broad discretion in that regard.^{wwwww} It follows that a scientific risk assessment carried out as thoroughly as possible on the basis of scientific advice founded on the principles of excellence, transparency and independence is an important procedural guarantee whose purpose is to ensure the scientific objectivity of the measures adopted and preclude any arbitrary measures.^{xxxx}

Ruling (factual outcome)

- The precautionary principle can (...) apply only in situations in which there is a risk, notably to human health, which, although it is not founded on mere hypotheses that have not been scientifically confirmed, has not yet been fully demonstrated.^{yyyy}
- It is appropriate to begin by observing that public health, which the contested regulation is intended to protect, must take precedence over economic considerations.^{zzzz}

The Court of first instance concludes to dismiss Pfizer's application as unfounded.

It is not completely clear what the relevance of this ruling is in respect of off-label use of medicines, as it deals predominantly with the powers of the Union institutions under the precautionary principle. The precautionary principle enables rapid response in the face of a possible danger to human health, for example by enforcing withdrawal from the market of products likely to be hazardous. This principle seems not to apply in case a medicinal product is used off-label outside the scope of an emergency situation (i.e. when there is no risk to human health).

Case T-74/00 *Artegoda and Others v Commission* - Judgment of the Court of 26 November 2002

Issue(s) at stake

The case of *Artegoda and Others v Commission* concerned the joined cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00 at the court of first instance. In these cases the competences of the *Commission* in the framework of marketing authorisations granted by national competent authorities are being discussed: was the Commission under the applicable legislation allowed to revoke national marketing authorisations on a centralised level? Furthermore, the burden of proof in respect of the benefit/risk-ratio was at stake: was it necessary for the

^{tttt} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 130.

^{uuuu} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 132.

^{vvvv} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 134.

^{wwww} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 170.

^{xxxx} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 172.

^{yyyy} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 146.

^{zzzz} T-13/99 *Pfizer Animal Health v Council* [2002], paragraph 471.



Commission to base its decision on new scientific evidence in respect of efficacy or safety?

Factual background

A number of medicinal products in the category of anorectics had been under scrutiny by the EU competent authorities for some time. On 9 March 2000, the Commission adopted, on the basis of article 15a of Directive 75/319,^{aaaaa} three decisions concerning an order to Member states to revoke the marketing authorisations of medicinal products for human use which contain Phentermine, Amfepramone, Clobenzorex, Fenbutrazate, Fenproporex, Mazindol, Mefenorex, Norpseudoephedrine, Phenmetrazine, Phendimetrazine or Propylhexedrine within 30 days. The contested decisions were justified by referring to the scientific conclusions which were appended to the CPMP final opinion of 31 August 1999 on the substance or substances concerned.^{bbbbb} The CPMP had concluded that a positive benefit-risk balance was lacking.^{cccc}

At the time of this ruling there was a general understanding that prior to the grant of a marketing authorisation it was up to the applicant to prove that a medicinal product meets the requirements for a marketing authorisation. Once the marketing authorisation is granted, the competent authorities have to prove that the risk/benefit ratio has changed in order to be able to revoke or vary the marketing authorisation. Furthermore, there were questions with respect to the Commission's power to revoke or vary national marketing authorisations.

Claims

The applicants claimed that the Court should:^{dddd}

- Annul the respective Commission Decisions;
- in the alternative, annul that decision in so far as article 1 thereof, in conjunction with Annex I thereto, requires the concerned member state to withdraw the marketing authorisation of the concerned medicinal product, marketed by the applicant;
- order the Commission to pay the costs.

Arguments of the parties

Applicants

The applicants submitted that the Commission was not competent to adopt the contested decisions. They claimed that the marketing authorisations of the medicinal products in question are purely national and that, consequently, article 15a of Directive 75/319 did not provide the Commission with a valid legal basis for taking those decisions. That article would only allow a Member State to initiate the Community decision-making procedure provided for in articles 13 and 14 of Directive 75/319 only in respect of authorisations granted in accordance with the provisions of Chapter III of that directive.^{eeee}

The applicants submitted that the aim of article 15a was to ensure that the harmonisation of medicinal products authorised through the mutual recognition

^{aaaaa} This is currently included article 30 of Directive 2001/83/EC and contains a referral procedure to the CHMP for arbitration in case of different decisions in member states in the assessment of the risk/benefit of a medicinal product.

^{bbbbb} T-74/00 *Artegodan and Others v Commission* [2002], paragraph 16.

^{cccc} T-74/00 *Artegodan and Others v Commission* [2002], paragraph 44, 59 and 72.

^{dddd} T-74/00 *Artegodan and Others v Commission* [2002], paragraph 84 to 92.

^{eeee} T-74/00 *Artegodan and Others v Commission* [2002], paragraph 94.



procedure is maintained if a subsequent amendment or the withdrawal of that marketing authorisation appears necessary to a Member State on grounds of protection of public health. In that system, marketing authorisations which have not been the subject of mutual recognition are purely national and therefore cannot, under any circumstances, be the subject-matter of a Community arbitration procedure under article 15a.^{ffff}

The applicants submitted that the contested decisions infringe article 11 of Directive 65/65 in three respects. First, they do not respect the rules of evidence laid down in that article. Under article 11 of Directive 65/65, the burden of proof of lack of therapeutic efficacy or harmfulness of an authorised substance lies with the competent authority. Furthermore, in the case of withdrawal of the marketing authorisation of a medicinal product, the lack of therapeutic efficacy or the harmfulness of that medicinal product in the normal conditions of use must be established beyond doubt, whereas, in the case of an application for authorisation, insufficient substantiation, which covers disagreement between scientists, may be grounds for refusing authorisation. In the present case, the CPMP and the Commission acted on the basis of mere doubts and transferred the burden of proof to the holders of the authorisations of the medicinal products in question.^{ggggg} Moreover, the applicants submitted that the criterion of long-term efficacy, on which the contested decisions are based, is not supported by new scientific data justifying withdrawal of the marketing authorisations of the medicinal products concerned.^{hhhhh}

Commission

The Commission submitted that it follows from the wording of article 15a of Directive 75/319, which expressly refers to authorisations granted in accordance with the provisions of Chapter III - which contains articles 8 to 15b -, that that article does not refer solely to marketing authorisations granted under the mutual recognition procedure provided for in article 9 of that directive but also covers marketing authorisations harmonised under article 12 of that directive.

The Commission accepted that under the first paragraph of article 11 of Directive 65/65 the onus was on it to prove that the substances in question lacked therapeutic efficacy. In the present case, contrary to the applicants' claims, the Commission did not consider that the applicants were required to demonstrate that the medicinal products containing the substances in question had a long-term effect. The CPMP's conclusion that the substances under consideration lacked efficacy was not based on mere doubts. On the contrary, it is apparent from the CPMP's scientific conclusions, annexed to the contested decisions, that, on the basis of the scientific data at its disposal, the CPMP carried out an analysis of the therapeutic effects of the substances in question, and concluded that they lacked efficacy on the ground that they appear to induce only modest, short-term weight-loss. There have been no controlled studies establishing that those substances have a relevant long-term influence on weight or provide a clinical benefit in the treatment of obesity. At the hearing, the Commission pointed out that it is not the task of the CPMP to carry out scientific studies in order to generate additional data.ⁱⁱⁱⁱ

Ruling (factual outcome)

^{ffff} T-74/00 *Artegoda and Others v Commission* [2002], paragraph 98.

^{ggggg} T-74/00 *Artegoda and Others v Commission* [2002], paragraph 157.

^{hhhhh} T-74/00 *Artegoda and Others v Commission* [2002], paragraph 159.

ⁱⁱⁱⁱ T-74/00 *Artegoda and Others v Commission* [2002], paragraph 165.



The court considered that, given the lack of any new scientific data or information relating to assessment of the efficacy of the substances in question, article 11 of Directive 65/65 precluded the competent authority from revising the positive assessment of the efficacy of the substances under consideration, which had been issued in 1996. It follows that, on any view, the contested decisions are in breach of the provisions of that article.^{jjjjj} The contested decisions therefore must be annulled in so far as they relate to the medicinal products marketed by the applicants.^{kkkkk}

Furthermore, even if the Commission had been competent to take the decisions, these would nevertheless be flawed on the ground of infringement of article 11. The Court finds that mere changes in a scientific criterion or, in more concrete terms, in good clinical practices - that is to say, therapeutic practices considered to be the most appropriate in the light of current scientific knowledge -, even if based on a consensus in the medical community, cannot on their own justify the withdrawal of a marketing authorisation of a medicinal product under article 11 of Directive 65/65 where those changes are not based on new scientific data or information.^{lllll} Moreover, the Court in any event reasoned that neither the CPMP Note for Guidance nor the national guidelines referred to in the CPMP opinions of 31 August 1999 established any new criterion for assessing the efficacy of a medicinal product in the treatment of obesity.^{mmmmm}

It is not completely clear what the relevance of this ruling is in respect of off-label use of medicines, as it deals predominantly with the power of the Commission to withdraw marketing authorisations.

Case C-62/09 Association of the British Pharmaceutical Industry v Medicines and Healthcare Products Regulatory Agency – Judgement of Judgment of the Court of 22 April 2010

Issues at stake

This case was referred to the Court of Justice for a preliminary ruling regarding the question whether a British financial incentive scheme implemented by the public authorities is covered by article 94(1) of Directive 2001/83/EC on promotion of medicinal products.

Factual background

The public authoritiesⁿⁿⁿⁿⁿ have – in their policy to reduce costs for pharmaceutical care – established a scheme, which encourages physicians to prescribe specific medicinal products. In this scheme the physicians are rewarded with financial incentives. The branch organisation of the pharmaceutical industry – ABPI – objects against this scheme because it could impact on the quality of the treatment of patients, because of the incentives – patients are not treated in the best possible manner. The ABPI furthermore found that the MHPR in establishing this scheme – acted against the rules prohibiting promotion of the use of (specified) medicinal products. The MHPR argued that article 4(3) of Directive 2001/83/EC clearly allows member states to take actions to control healthcare costs. The High Court decided to stay the proceedings and to refer the following questions to the Court of Justice.

^{jjjjj} T-74/00 *Artegodan and Others v Commission* [2002], paragraph 220.

^{kkkkk} T-74/00 *Artegodan and Others v Commission* [2002], paragraph 221.

^{lllll} T-74/00 *Artegodan and Others v Commission* [2002], paragraph 211.

^{mmmmm} T-74/00 *Artegodan and Others v Commission* [2002], paragraph 212.

ⁿⁿⁿⁿⁿ Primary Care Trusts (PCTs) and Local Health Boards (LHBs)



Does Article 94(1) of Directive 2001/83/EC preclude a public body forming part of a national public health service, in order to seek to reduce its overall expenditure on medicines, from implementing a scheme which offers financial incentives to medical practices (which may in turn provide a financial benefit to the prescribing doctor) to prescribe a specific named medicine supported by the incentive scheme that is either:

- a) a different prescription medicine to the medicine previously prescribed by the doctor to the patient; or
- b) a different prescription medicine to that which otherwise might have been prescribed to the patient but for the incentive scheme, where such a different prescription medicine is from the same therapeutic class of medicines used for treatment of the patient's particular condition?"

Arguments of the parties

"The ABPI and the European Commission submit that Article 94(1) of Directive 2001/83 also applies to national authorities. Consequently, that provision precludes a public body forming part of a national public health service from implementing a scheme which offers financial inducements to medical practices in order that the doctors in those practices prescribe a specific named medicinal product, even if the aim of that scheme is to reduce overall public expenditure on medicinal products^{oooo}."

"By contrast, the United Kingdom, Czech, Estonian, Spanish, French and Netherlands Governments consider that, as is apparent from the broad logic of Directive 2001/83 and since Article 152(5) EC expressly provides that European Community action in the field of public health is to fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care, Article 94 of the directive does not cover the competent national public health authorities. In addition, even if the prohibition in Article 94 were applicable to such authorities, a financial incentive scheme set up by them would fall within the derogation provided for in Article 4(3) of the directive since such a scheme aims to ensure access for all to a sufficient quantity of medicinal products at a reasonable price^{pppp}."

Ruling (Factual Outcome)

The Court clarifies that Article 94(1) is intended to prohibit inducement of healthcare professionals to act in accordance with economic interests when prescribing or supplying medicinal products: promotion of medical and pharmaceutical practice should comply with rules of professional conduct^{qqqq}. However, as health policies defined by a Member State and the public expenditure devoted to it do not any profit-making or commercial purposes, the prohibition of promotion of medicines does not apply to the public authorities^{rrrr}.

"In those circumstances, it is permissible for those authorities, in the exercise of the responsibilities which they assume, to determine, on the basis of evaluations of the therapeutic qualities of medicinal products by reference to their cost for the public budget, whether, in order to treat certain conditions, certain medicinal products

^{oooo} Case C-62/09 *Association of the British Pharmaceutical Industry v Medicines and Healthcare Products Regulatory Agency* [2010], paragraph 25.

^{pppp} Case C-62/09 *Association of the British Pharmaceutical Industry v Medicines and Healthcare Products Regulatory Agency* [2010], paragraph 26.

^{qqqq} Case C-62/09 *Association of the British Pharmaceutical Industry v Medicines and Healthcare Products Regulatory Agency* [2010], paragraph 27 to 30.

^{rrrr} Case C-62/09 *Association of the British Pharmaceutical Industry v Medicines and Healthcare Products Regulatory Agency* [2010], paragraph 32 to 34.



containing a given active substance are, from the point of view of public finances, preferable to other medicinal products containing a different active substance, but falling within the same therapeutic class^{sssss}."

The ruling of the Court of Justice is that Article 94(1) does not preclude financial incentive schemes (...) implemented by national public health authorities in order to reduce their public-health expenditure and designed to encourage, for the purpose of treating certain conditions, the prescription by doctors of specific named medicinal products containing an active substance which is different from the active substance of the medicinal product which was previously prescribed or which might have been prescribed but for such an incentive scheme^{tttt}.

It is not completely clear what the relevance of this ruling is in respect of off-label use of medicines. The ruling does not specifically refer to the situation where, in case of financial incentive scheme, a medicinal product used off-label is preferable to other medicinal products. It only speaks of medicinal products containing a different active substance, but falling within the same therapeutic class.

Case C-249/09 Novo Nordisk AS v Ravimiamet - Judgment of the Court of 5 May 2011

Issue(s) at stake

The case of *Novo Nordisk AS v Ravimiamet* concerned the relationship between the official product information and claims made in advertisements; the interpretation of article 87(2) of Directive 2001/83/EC. It followed upon a reference for a preliminary ruling by the Estonian court Tartu ringkonnakohus.

Factual background

Novo Nordisk A/S ("Novo Nordisk") advertised its product Levemir in a medical journal with some claims which were – according to the national Estonian competent authority Raviamet – contrary to the authorised text in the Summary of Product Characteristics ("SmPC"). Raviamet ordered Novo Nordisk to withdraw the advertisement. The advertisement contained the following claims:^{uuuuu}

- Effective blood sugar control with lower risk of hypoglycaemia;
- Body weight of 68% of patients does not increase or even decreases;
- 82% of patients inject Levemir (insulin detemir) once a day in clinical practice.

From the SmPC appears:^{vvvv}

- hypoglycaemia is precisely the most frequent side effect of Levemir;
- comparative tests with NPH insulin and insulin glargine showed that body weight rose slightly or not at all in the Levemir group, and
- Levemir is taken once or twice a day.

The Raviamet found that the concerned advertisement is unlawful in that:^{wwwww}

- it does not state that the risk of hypoglycaemia is lower at night;

^{sssss} Case C-62/09 *Association of the British Pharmaceutical Industry v Medicines and Healthcare Products Regulatory Agency* [2010], paragraph 35.

^{tttt} Case C-62/09 *Association of the British Pharmaceutical Industry v Medicines and Healthcare Products Regulatory Agency* [2010], paragraph 42.

^{uuuuu} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 14.

^{vvvvv} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 15.

^{wwwww} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 16.



- it claims that body weight falls, which is not stated in the summary of product characteristics, and
- the figure of 82% that is cited does not appear in the summary of product characteristics.

Novo Nordisk brought an action for annulment of this decision before the Tartu court, claiming inter alia that the purpose of advertising a medicinal product to persons who are entitled to prescribe medicines is to disseminate to those persons supplementary information based on data published in scientific journals, and that it is therefore lawful to use quotations from medical and scientific literature which are not expressly stated in the summary of product characteristics.^{xxxxx} The Tartu court dismissed the action. It pointed out, in particular, that under Article 87(2) of Directive 2001/83/EC, all parts of an advertisement for a medicinal product must comply with the information in the summary of product characteristics and that neither Articles 91(1) and 92(1) of Directive 2001/83/EC, nor recital 47 in the preamble to that directive, provide that information about the medicinal product which does not appear in the summary may be included in an advertisement for a medicinal product.^{yyyyy} That judgment was appealed to the referring court, which referred the case to the Court of Justice and asked:

1. Must Article 87(2) of Directive 2001/83 (...) be interpreted as extending also to quotations taken from medical journals or other scientific works which are included in advertisements for medicinal products directed to persons qualified to prescribe medicines?
2. Must Article 87(2) of Directive 2001/83 be interpreted as prohibiting the publication in advertisements for medicinal products of claims which conflict with the summary of product characteristics, but not requiring that all the claims in advertisements for medicinal products must be included in the summary of product characteristics or be derivable from information in the summary?

Arguments of the parties

In respect of the first question Ravimiamet and all intervening member states, Estonia, Belgium, Czech republic, Poland and Portugal, state that article 87(2) applies to all advertising and not only when it is directed at the general public. The main argument for this position is that it follows from the structure of the Directive,^{zzzzz} as well as from the aim of the Directive, namely to protect public health:^{aaaaaa}

“Article 87 of Directive 2001/83 seeks to uphold that objective (protection of public health) through the regulation of advertising for medicinal products, first, by prohibiting or limiting the use of information that could mislead the recipient or is inaccurate or unfounded, which could lead to misuse of a medical product and, second, by requiring that certain essential information be provided.”^{bbbbbb}

“As all of the intervening Member States pointed out, those rules also apply to all parts of advertisements directed at persons qualified to prescribe or supply medicinal products, since, in that type of advertising too, incorrect or incomplete information can clearly endanger people’s health and thus jeopardise the fundamental objective pursued by Directive 2001/83.”^{cccccc}

^{xxxxx} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 17.

^{yyyyy} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 18.

^{zzzzz} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 22 to 31.

^{aaaaaa} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 33 to 34.

^{bbbbbb} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 33.

^{cccccc} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 34.



To answer the second question, the Court started to consider that the legislator did not specify in Article 87(2), that all the information in the advertising of a medicinal product must be identical to that contained in the SmPC. That provision requires only that that information must comply with the SmPC.^{ddddd} From the system and objective, the preamble and other provisions of the of the directive, the Court concluded:

“In order to contribute, in accordance with recital 47 in the preamble to Directive 2001/83, to the information available to persons qualified to prescribe or supply medicinal products, and taking account of the greater level of scientific knowledge of those persons compared with the general public, advertising of medicinal products to such persons may, therefore, include information that is compatible with the summary of product characteristics, that confirms or clarifies the specifications contained in that summary, pursuant to Article 11 of the Directive, provided that the additional information is consistent with the requirements of Articles 87(3) and 92(2) and (3) of the Directive.”^{eeeeee}

“In other words, such information, firstly, may not be misleading and is to encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties. Secondly, it must be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to form his or her own opinion of the therapeutic value of the medicinal product concerned. Finally, quotations, tables and other illustrative matter taken from medical journals or other scientific works are to be clearly identified and the precise sources indicated, so that health professionals are informed of them and can verify them.”^{ffffff}

CJEU Ruling (factual outcome)

Firstly, article 87(2) of Directive 2001/83/EC (...) must be interpreted as extending also to quotations taken from medical journals or other scientific works which are included in advertisements for medicinal products directed at persons qualified to prescribe or supply medicines.

Secondly, article 87(2) of Directive 2001/83/EC must be interpreted as prohibiting the publication, in advertising of medicinal products directed at persons qualified to prescribe or supply them, of claims which conflict with the summary of product characteristics, but it does not require that all the claims in such advertisements are included in that summary or can be derived from it. Such advertisements may include claims supplementing the information referred to in Article 11 of that directive, provided that those claims:

- confirm or clarify – and are compatible with – that information, and do not distort it,
- and are consistent with the requirements of Articles 87(3) and 92(2) and (3) of that directive.

In respect of the issue of off-label use the present ruling explains that the holder of a marketing authorisation or any other person may make claims in respect of a medicinal product, as long as these are accurate, up-to-date, et cetera, and as long as these claims do not conflict with the SmPC. In other words: claims for off-label use, even well-documented, are not acceptable.

^{ddddd} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 43.

^{eeeeee} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 49.

^{ffffff} C-249/09 *Novo Nordisk AS v Ravimiamet* [2011], paragraph 50.



Case C-185/10 European Commission v Republic of Poland – Judgment of the Court of 29 March 2012Issue(s) at stake

Commission v Poland concerned the scope of the exemption for named patient supply in article 5 (1) of Directive 2001/83/EC and specified the meaning of ‘special need’ in the aforementioned provision.⁹⁹⁹⁹⁹⁹

The European Commission asked the Court to declare that, *“by adopting and maintaining in force Article 4 of the Law on Medicinal Products (Prawo farmaceutyczne) [...] inasmuch as that statutory provision dispenses with the requirement for a marketing authorisation for medicinal products from abroad which have the same active substances, the same dosage and the same form as those having obtained a marketing authorisation in Poland, on condition that, in particular, the price of those imported medicinal products is competitive in relation to the price of products having obtained such authorisation, the Republic of Poland has failed to fulfil its obligations under Article 6 of Directive 2001/83/EC [...]”*.^{hhhhh}

Factual background

The Polish Law on Medicinal Products contained a provision that allowed medicinal products to be imported into Poland without a marketing authorisation on two conditions. The first condition was that the imported medicinal product should have the same active substances, the same dosage and the same form as a medicinal product authorised in Poland. Secondly, in particular the price of the imported medicinal products needed to be competitive compared to the price in Poland.

Arguments of the parties

The European Commission asked the court to declare that Poland had failed to fulfil its obligations under Article 6 (1) of Directive 2001/83/EC, while Poland argued that the provision in their law was within the scope of article 5 (1) of the Directive.

The Commission considered that *“Directive 2001/83 does not provide for the possibility of placing medicinal products on the market having regard to their ‘competitive’ price, when they have not, also, obtained the authorisation referred to in Article 6 of that directive, issued by the national authorities or in accordance with the centralised procedure provided for in Regulation No 726/2004.”*ⁱⁱⁱⁱⁱⁱ

The Commission argued that article 5(1) of Directive 2001/83 allows for a derogation from the requirement to have a national marketing authorisation for a particular medicinal product *“where the medicinal product is supplied on account of a specific individual order and, not being on the national market, has to be imported, but it does not, in contrast, justify a derogation based on financial reasons.”*^{jjjjj} The Commission added that *“the possibility offered by the Polish legislation is not limited to the importation of medicinal products necessary in the course of treating specific problems which affect certain patients in particular, but concerns, in particular, medicinal products used for treating persons who cannot leave their place of care, so that the derogation at issue is capable of relating to patients of an entire hospital sector or to wholesale marketing. It points out, furthermore, that Article 4(3a) of the Law on*

⁹⁹⁹⁹⁹⁹ C-185/10 *Commission v Poland* [2012].

^{hhhhh} C-185/10 *Commission v Poland* [2012], paragraph 1.

ⁱⁱⁱⁱⁱⁱ C-185/10 *Commission v Poland* [2012], paragraph 12.

^{jjjjj} C-185/10 *Commission v Poland* [2012], paragraph 13.



Medicinal Products does not refer to the medical opinion in an individual case, but only to 'the requirement ... expressed by a health insurance doctor'. That provision therefore authorises not the importation of solely a limited quantity of a medicinal product such as to cover only individual needs, but importation on a larger scale of medicinal products the price of which is 'competitive' in relation to that of medicinal products available on the national market. „kkkkkk

In contrast the Republic of Poland contested the merits of the allegation of failure to fulfil obligations. The Republic of Poland contended that the disputed provision of its national law complied with the derogation provided for in Article 5(1) of Directive 2001/83.^{lllll}

According to the Republic of Poland, the Commission had overlooked the conditions which arise from an overall analysis of Article 4 of the Law on Medicinal Products. The exemption only applied under the fulfilment of a number of strict conditions, which are even more strict than the conditions set by Article 5(1) of Directive 2001/83.^{mmmmm} The Polish provision excludes, in principle, the possibility of importing medicinal products containing the same active substance or substances and the same dosage, “unless their price is competitive in relation to the price of the medicinal product which has obtained a marketing authorisation and on condition, first, that the requirement expressed by a health insurance doctor has been confirmed by a consultant in the medical sector concerned, and, second, that the minister with responsibility for health-related matters has expressly decided to authorise the importation.”ⁿⁿⁿⁿⁿ

The Republic of Poland maintained that “article 5(1) of Directive 2001/83 does not lay down a condition of unavailability of a medicinal product on the national market in the sense of the lack of an ‘equivalent’ registered medicinal product.”^{ooooo} Moreover the Republic of Poland argued that “the derogation provided for in [the disputed national provision] the Law on Medicinal Products from the requirement that a marketing authorisation be obtained is based not on the lower price of the medicinal product abroad, but on the need to import a medicinal product where it is necessary for the purpose of saving the life or safeguarding the health of a patient. That objective satisfies the condition of fulfilling special needs set out in Article 5(1) of Directive 2001/83.”^{ppppp}

The Republic of Poland also maintained that “a decision to import a medicinal product in the context of health insurance can be dictated by financial considerations, namely by the need to ensure the financial stability of the national health insurance system. It points out in that regard that, according to Article 168(7) TFEU, EU law does not detract from the power of the Member States to organise their social security systems and to adopt, in particular, measures intended to govern the consumption of pharmaceutical products in order to promote the financial stability of their health-care insurance schemes. Similarly, it notes that Article 4(3) of Directive 2001/83 provides that the directive's provisions are not to affect the powers of the Member States' authorities either as regards the setting of prices for medicinal

kkkkk C-185/10 *Commission v Poland* [2012], paragraph 14.

lllll C-185/10 *Commission v Poland* [2012], paragraph 16.

mmmmm C-185/10 *Commission v Poland* [2012], paragraph 17 and 18.

nnnnn C-185/10 *Commission v Poland* [2012], paragraph 18

ooooo C-185/10 *Commission v Poland* [2012], paragraph 19.

ppppp C-185/10 *Commission v Poland* [2012], paragraph 20.



products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions. ^{“qqqqqq}

“Finally, the Republic of Poland claims, first, that Article 4(3a) of the Law on Medicinal Products is used in rare and exceptional cases and, second, that the basic criterion for authorising the importation of a medicinal product is the safety of the patient and the concern of guaranteeing him a real possibility of obtaining the treatment which is necessary for his survival or health; the competitive nature of the price of that treatment in relation to that of equivalent medicinal products registered in Poland constitutes only a supplementary condition. In a situation where a number of patients have only limited financial means, the importation of an equivalent but less expensive medicinal product is the only possibility of treating those persons, even of saving their life, and this certainly satisfies the condition concerning the need to ‘fulfil special needs’ provided for in Directive 2001/83. ”rrrrrr

CJEU Ruling (factual outcome)

The court stated that as a general rule, article 6 (1) of Directive 2001/83/EC provides that no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued. ^{ssssss} This requirement is intended to fulfil the objectives of Directive 2001/83/EC: the elimination of hindrances to trade in medicinal products between the Member States and the protection of public health. ^{tttttt} Subsequently, the court established that the exemption to that requirement under article 5 (1) of the directive should be interpreted restrictively and its application *“must remain exceptional in order to preserve the practical effect of the marketing authorisation procedure”* ^{uuuuuu} and should only be used *“if that is necessary, taking account of the specific needs of patients.”* ^{vvvvvv}

The court subsequently clarified the requirements of a ‘special need’ and a ‘bona fide unsolicited order’ in article 5 (1). The concept of ‘special needs’ *“applies only to individual situations justified by medical considerations and presupposes that the medicinal product is necessary to meet the needs of the patient.”* ^{wwwwww} Next, a ‘bona fide unsolicited order’ means *“the medicinal product must have been prescribed by the doctor as a result of an actual examination of his patients and on the basis of purely therapeutic considerations.”* ^{xxxxxx}

Moreover, as the court considered, article 5 (1) *“can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market.”* ^{yyyyyy} No such special need exists if there are already authorised medicinal products available on the national market with the same active substances, the same dosage and the same form. ^{zzzzzz} Furthermore, financial considerations do not lead to a special need. ^{aaaaaa}

^{qqqqqq} C-185/10 *Commission v Poland* [2012], paragraph 24.

^{rrrrrr} C-185/10 *Commission v Poland* [2012], paragraph 25.

^{ssssss} C-185/10 *Commission v Poland* [2012], paragraph 26.

^{tttttt} C-185/10 *Commission v Poland* [2012], paragraph 27.

^{uuuuuu} C-185/10 *Commission v Poland* [2012], paragraph 32 and 48.

^{vvvvvv} C-185/10 *Commission v Poland* [2012], paragraph 33.

^{wwwwww} C-185/10 *Commission v Poland* [2012], paragraph 34.

^{xxxxxx} C-185/10 *Commission v Poland* [2012], paragraph 35.

^{yyyyyy} C-185/10 *Commission v Poland* [2012], paragraph 36.

^{zzzzzz} C-185/10 *Commission v Poland* [2012], paragraph 37.

^{aaaaaa} C-185/10 *Commission v Poland* [2012], paragraph 38.



Consequently, the contested provision in the Polish Law did not satisfy the conditions to benefit from the derogation in article 5 (1) of Directive 2001/83/EC.^{bbbbbb} Therefore, the court ruled that the Republic of Poland had failed to fulfil its obligations under article 6 of Directive 2001/83/EC.^{cccccc}

The court established that the derogation from the need for a marketing authorisation requirement through named patient supply should remain exceptional to preserve the practical effect of the marketing authorisation. It may only be exercised if necessary taken into account the specific needs of patients. The court did not comment on derogations from an already granted marketing authorisation, as is the case in off-label use.

In the end, the court declared that *“by adopting and maintaining in force Article 4 of the Law on Medicinal Products (Prawo farmaceutyczne) [...] inasmuch as that statutory provision dispenses with the requirement for a marketing authorisation for medicinal products from abroad which have the same active substances, the same dosage and the same form as those having obtained a marketing authorisation in Poland, on condition that, in particular, the price of those imported medicinal products is competitive in relation to the price of products having obtained such authorisation, the Republic of Poland has failed to fulfil its obligations under Article 6 of Directive 2001/83/EC [...]”*.^{ddddd}

Case C-535/11 Novartis Pharma v Apozyt – Judgment of the Court of 11 April 2013

Issue(s) at stake

The case of *Novartis Pharma v Apozyt* concerned the request for a preliminary ruling on the interpretation of Article 3(1) of Regulation (EC) No 726/2004 from the Landgericht Hamburg (Germany). The request has been made in proceedings between Novartis Pharma GmbH and Apozyt GmbH concerning whether Apozyt may produce, distribute and promote ready-to-use syringes that are intended for the treatment of eye disease and contain doses of the medicinal products Lucentis and Avastin. These are two centrally authorised products, Lucentis and Avastin, which both contain as active substance a growth inhibitor. Both products are currently used in the EU to treat patients with wet age-related macular degeneration (AMD), even if only Lucentis is authorised for this indication. Avastin, being the older of the two products, was used to treat AMD "off label" before Lucentis became available. It is continued to be used in several Member States for that purpose, since it may be purchased at lower price. The referring court asked, in essence, whether activities such as those at stake in the proceedings require a marketing authorisation under Article 3 (1) of Regulation (EC) No 726/2004,^{eeeeee} which determines the scope of products eligible to the centralised procedure and, if not, whether these activities remain subject to Directive 2001/83. In particular, the case focused on whether medicinal products developed by biotechnological processes and authorised through the centralised procedure would require a new marketing authorisation after being repackaged from vials into ready-to-use syringes.^{ffffff}

^{bbbbbb} C-185/10 *Commission v Poland* [2012], paragraph 43.

^{cccccc} C-185/10 *Commission v Poland* [2012], paragraph 52.

^{ddddd} C-185/10 *Commission v Poland* [2012].

^{eeeeee} C-535/11 *Novartis v Apozyt* [2013].

^{ffffff} C-535/11 *Novartis v Apozyt* [2013], paragraph 33.



Factual background

Novartis is the marketing authorisation holder for Lucentis, which is authorised under article 3 (1) of Regulation (EC) No 726/2004 for, amongst other things, the treatment of wet age-related macular degeneration, a serious eye disorder.^{ggggggg} Lucentis is distributed in vials that are sold for around 1,200 Euro per unit. Each vial is intended for the administration of a single dose, even though a physician administers only 0.05 ml out of 0.23 ml of the medicinal liquid in the vial.^{hhhhhh} Roche Pharma AG, which is not a party to the main proceedings, is the marketing authorisation holder for Avastin which is, also under article 3 (1), approved for the treatment of several types of cancer.ⁱⁱⁱⁱⁱⁱ The use of Avastin requires some preparation, which is commonly performed by a hospital pharmacy.

Apozyt prepared, using the content of the medicinal products Lucentis and Avastin, pre-filled syringes with the exact amount as prescribed by physicians. The pre-filled syringes were delivered to pharmacies, which had ordered the syringe on prescription for a patient. The Apozyt's method allowed the vials of Lucentis and Avastin to be used for multiple injections and at a considerably lower price than Lucentis and Avastin.^{jjjjjj}

Arguments of the parties

Novartis and Apozyt disagreed about whether Apozyt's syringes required a marketing authorisation in accordance with article 3 (1) of Regulation (EC) No 726/2004.^{kkkkkk} Novartis argued that the activities of Apozyt amounted to acts of unfair competition.^{llllll} Novartis contended that a marketing authorisation was required for the activities of Apozyt since the active substances in Lucentis and Avastin have been developed by means of recombinant DNA technology and are also obtained using hybridoma and monoclonal antibody methods.^{mmmmmm} Moreover, Novartis claimed that the surplus content is accounted for by production procedures and is needed for safety reasons. Novartis maintained that there is a danger of infiltration of bacteria when the original product is transferred from one container to another, as well as a problem relating to the conservation of the product in ready-to-use syringes as done by Apozyt.ⁿⁿⁿⁿⁿⁿ The position of Novartis is supported by the Czech and Greek Governments.^{oooooo} Apozyt contended that their activities could be regarded as the 'development' of a medicinal product because the production process of Lucentis and Avastin - that are the subject of a marketing authorisation - has already been completed when Apozyt re-packages the medicines into ready-to-use syringes. Furthermore, Apozyt submitted that their preparation under sterile conditions guarantees a higher degree of safety compared to given the preparation by doctors themselves. The syringes used by Apozyt are the same as those supplied by Novartis and Roche, so that issue cannot be taken with Apozyt for altering the process for administering the medicinal products in question.^{pppppp} The position of Apozyt is supported by the German Government, Ireland and the Portuguese Government.^{qqqqqq}

^{ggggggg} C-535/11 *Novartis v Apozyt* [2013], paragraph 18 and 19.

^{hhhhhhh} C-535/11 *Novartis v Apozyt* [2013], paragraph 20.

ⁱⁱⁱⁱⁱⁱⁱ C-535/11 *Novartis v Apozyt* [2013], paragraph 21 and 22.

^{jjjjjjj} C-535/11 *Novartis v Apozyt* [2013], paragraph 23.

^{kkkkkkk} C-535/11 *Novartis v Apozyt* [2013], paragraph 24 to 26.

^{lllllll} C-535/11 *Novartis v Apozyt* [2013], paragraph 24.

^{mmmmmmm} C-535/11 *Novartis v Apozyt* [2013], paragraph 24.

ⁿⁿⁿⁿⁿⁿⁿ C-535/11 *Novartis v Apozyt* [2013], paragraph 25.

^{ooooooo} C-535/11 *Novartis v Apozyt* [2013], paragraph 34.

^{ppppppp} C-535/11 *Novartis v Apozyt* [2013], paragraph 26.

^{qqqqqqq} C-535/11 *Novartis v Apozyt* [2013], paragraph 35



Furthermore, the Commission contended that the question raised may be of no relevance for the resolution of the dispute in the main proceedings, since, in its view, the word 'hergestellt' (developed) in the introductory words of the German-language version of point 1 of the Annex to Regulation No 726/2004 cannot be construed as a means of determining whether the obligation to hold a marketing authorisation also applies to activities whereby portions of a medicinal product which has been developed and produced in accordance with authorised procedures are, on a doctor's prescription, subsequently transferred into another container. The Commission also maintained that, in order to decide on the case before it, the referring court must in reality ascertain whether activities such as those at issue in the main proceedings, whereby ready-to-use syringes are filled with a medicinal product which is already authorised and is contained in perforable vials, must be regarded as processes involving dividing up or changes in packaging or presentation within the meaning of Article 40(2) of Directive 2001/83. If that is the case, Apozyt would not need a marketing authorisation to carry out such processes. If, however, such processes could not be regarded as falling within Article 40 of that directive, that would be a strong indication that a marketing authorisation is necessary to carry them out.

CJEU Ruling (factual outcome)

The court observed that article 3 (1) of Regulation (EC) No 726/2004 established an obligation to apply for a marketing authorisation in the framework of the centralised procedure for high-technology medicinal products developed by specific biotechnological processes,^{rrrrrrr} such as Lucentis and Avastin.^{sssssss} However, the court determined that the activity of Apozyt cannot *"be equated with a new placing on the market of a medicinal product"*,^{ttttttt} and accordingly, Apozyt *"in that respect, [is] not subject to the obligation to hold a marketing authorisation granted by (...) article 3 (1) of the regulation"*,^{uuuuuuu} provided *"that the processes in question do not result in any modification of the medicinal product and that they are carried out solely on the basis of individual prescriptions making provision for them"*.^{vvvvvvv}

Nevertheless, the court concluded that the activity of Apozyt remained *"subject to the provisions of Directive 2001/83, in particular the provisions laying down a requirement for authorisation to manufacture medicinal products"*.^{wwwwwww} The German government pointed out that it had applied article 5(1) of Directive 2001/83/EC to derogate from the directive.^{xxxxxxx} In this respect, the court confirmed its reasoning in *Commission v Poland*.^{yyyyyyy} The court reasoned that *"It should be borne in mind in that regard that Article 5(1) of Directive 2001/83 is a specific derogating provision, which must be interpreted strictly, applicable in exceptional cases where it is appropriate to meet special medical needs, in circumstances in which a doctor, following an actual examination of his patients and on the basis of purely therapeutic considerations, prescribes a medicinal product which does not have a valid marketing authorisation in the European Union and for which there is no authorised equivalent on the national market or which is unavailable on that market (see, to that effect, Case C-185/10 Commission v Poland [2012] ECR, paragraphs 35, 36 and 48)."*^{zzzzzzz} In *Commission v*

^{rrrrrrr} C-535/11 Novartis v Apozyt [2013], paragraph 37.

^{sssssss} C-535/11 Novartis v Apozyt [2013], paragraph 40.

^{ttttttt} C-535/11 Novartis v Apozyt [2013], paragraph 42.

^{uuuuuuu} C-535/11 Novartis v Apozyt [2013], paragraph 42.

^{vvvvvvv} C-535/11 Novartis v Apozyt [2013], paragraph 42.

^{wwwwwww} C-535/11 Novartis v Apozyt [2013], paragraph 44.

^{xxxxxxx} C-535/11 Novartis v Apozyt [2013], paragraph 45.

^{yyyyyyy} C-185/10 Commission v Poland [2012]; C-535/11 Novartis v Apozyt [2013], paragraph

46.

^{zzzzzzz} C-535/11 Novartis v Apozyt [2013], paragraph 46.



Poland the Court had pointed out that *"in particular, in paragraph 37 of that judgment, that Article 5(1) cannot be relied on where medicinal products having the same active substances, the same dosage and the same form as those which the doctor providing treatment considers that he must prescribe to treat his patients are already authorised and available on the national market."*^{aaaaaaa}

Subsequently, the court considered that in the circumstances of the present case, article 5(1) of Directive 2001/83/EC cannot be relied on with regard to the use of a medicinal product such as Lucentis, *"since those circumstances do not entail prescription of a medicinal product different from the product which already has a marketing authorisation; the injection volumes used are no different from those provided for in the marketing authorisation and nor is the product used for a therapeutic indication not covered by the marketing authorisation."*^{bbbbbbb}

However, as the court continued, *"the possibility remains that the Federal Republic of Germany may be able to rely on Article 5(1) of Directive 2001/83 as regards the making available of an authorised medicinal product, such as Avastin, for therapeutic indications not covered by the marketing authorisation, where such a formulation is in accordance with the specifications of an authorised practitioner and is for use by an individual patient under his direct personal responsibility. Indeed, in that regard, since the active ingredients of Avastin and Lucentis are different, a doctor, when faced with a particular condition and relying solely on therapeutic considerations specific to his patients, including considerations pertaining to how the medicine is administered, may take the view that a treatment not covered by the marketing authorisation, in accordance with the pharmaceutical form and the dosage which he considers appropriate and using Avastin which has a Community marketing authorisation, is preferable to treatment with Lucentis."*^{ccccccc}

"Concerning the last point, it should, however, be recalled that a prescribing doctor is required, from the point of view of professional conduct, not to prescribe a given medicinal product if it is not appropriate for the therapeutic treatment of his patient, including from the point of view of how it is administered."^{ddddddd}

The court ruled that *"activities such as those at issue in the main proceedings, provided that they do not result in a modification of the medicinal product concerned and are carried out solely on the basis of individual prescriptions calling for processes of such a kind – a matter which falls to be determined by the referring court –, do not require a marketing authorisation under Article 3(1) of Regulation (EC) No 726/2004 [...], but remain, in any event, subject to Directive 2001/83/EC [...]"*^{eeeeeee}

Finally the court considered the need for a manufacturing license as in article 40 of Directive 2001/83/EC. Under the first subparagraph of Article 40(2) authorisation is indeed required as far as it concerns the repackaging of medicinal products which have a marketing authorisation.^{ffffff} However, as Ireland and the Commission submitted, *"under the second subparagraph of Article 40(2) of Directive 2001/83 such authorisation is not required for, inter alia, dividing up and changes in packaging where those processes are carried out, solely for retail supply, by pharmacists in*

^{aaaaaaa} C-535/11 Novartis v Apozyt [2013], paragraph 46.

^{bbbbbbb} C-535/11 Novartis v Apozyt [2013], paragraph 47.

^{ccccccc} C-535/11 Novartis v Apozyt [2013], paragraph 48.

^{ddddddd} C-535/11 Novartis v Apozyt [2013], paragraph 49.

^{eeeeeee} C-535/11 Novartis v Apozyt [2013].

^{ffffff} C-535/11 Novartis v Apozyt [2013], paragraph 51.



dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes.”^{gggggggg} The latter is for the referring court to ascertain.^{hhhhhhh}

The relevance of this ruling for off-label use of a medicinal product is unclear, since the ruling deals with the need to obtain a marketing authorisation and any exemptions to this requirement.

Case C-179/16 Request for a preliminary ruling from the Consiglio di Stato (Italy) lodged on 25 March 2016 — F. Hoffmann-La Roche AG, La Roche SpA, Novartis AG and Novartis Farma SpA v Autorità Garante della Concorrenza e del Mercato

Issue at stake

Court case C-179/16, where the Italian supreme court has asked EU Court of Justice for a precedent decision on a case where Italian competition office has set 90 million penalty both to Hoffmann-La Roche and Novartis due to an illegal cartel concerning licensing agreement of Avastin and Lucentis products.

According to today’s Official Journal (OJ [2006] C222), the Italian Council of State has asked:

1. On a proper construction of Article 101 TFEU, can the parties to a licensing agreement be regarded as competitors if the licensee company operates on the relevant market concerned solely by virtue of that agreement? Do possible restrictions of competition between the licensor and the licensee in such a situation, although not explicitly provided for in the licensing agreement, fall outside the scope of Article 101(1) TFEU or fall within the scope of the exception set out in Article 101(3) TFEU and, if so, within what limits?

2. Does Article 101 TFEU allow the National Competition Authority to define the relevant market autonomously vis-à-vis the content of marketing authorisations (MAs) for medicinal products granted by the competent pharmaceutical regulatory authorities (the Agenzia Italiana del Farmaco and the European Medicines Agency), or must the relevant market for the purposes of Article 101 TFEU instead be held to be primarily shaped and established in respect of the authorised medicinal products by the appropriate regulatory authority in a way binding on the National Competition Authority also?

3. In the light of the provisions of Directive 2001/83/EC, [...] in particular Article 5 thereof, which relates to marketing authorisations for medicinal products, does Article 101 TFEU allow a medicinal product used off-label and a medicinal product that has received an MA in respect of the same therapeutic indications to be regarded as interchangeable and, thus, to be included in the same relevant market?

4. Pursuant to Article 101 TFEU, for the purposes of defining the relevant market, is it important to establish, in addition to the essential fungibility of pharmaceutical

^{gggggggg} C-535/11 Novartis v Apozyt [2013], paragraph 52.

^{hhhhhhh} C-535/11 Novartis v Apozyt [2013], paragraph 53.



products on the demand side, whether or not those products have been supplied on the market in accordance with the regulatory framework concerning the marketing of medicinal products?

5. In any event, can a concerted practice intended to emphasise that a medicinal product is less safe or less effective be regarded as intended to restrict competition, when the idea that that product is less effective or less safe, although not supported by reliable scientific evidence, cannot, in the light of the level of scientific knowledge available at the time of the events in question, be indisputably excluded either?

Case T-452/14 Laboratoires CTRS v European Commission Judgment of the Court of 11 June 2015

Issue(s) at stake

In *Laboratoires CTRS v Commission*, the General Court reflected on off-label prescribingⁱⁱⁱⁱⁱⁱⁱ in EU law.^{jjjjjjj} The case itself concerned the application for an annulment in part of a Commission decision granting, in exceptional circumstances, a marketing authorisation under Regulation (EC) No 726/2004 for 'Cholic Acid FGK — cholic acid', an orphan medicinal product (which was later renamed Kolbam) and amending the marketing authorisation granted in exceptional circumstances for 'Kolbam — cholic acid', an orphan medicinal product for human use, in so far as that decision in substance indicates that that medicinal product is authorised for the therapeutic indications for Orphacol or, in the alternative, for annulment of Article 1 of the decision to grant the marketing authorisation. ASK Pharmaceuticals GmbH, the marketing authorisation holder of Kolbam, acted as an intervener in support of the European commission.

Factual background

Laboratoires CTRS is the marketing authorisation holder for Orphacol, an orphan medicinal product. Orphan medicinal products are products for rare diseases and, as an incentive to their development, the marketing authorisation holder is granted a ten year market exclusivity.^{kkkkkkkk} Within a year after authorising Orphacol, the European Commission also authorised the orphan medicinal product Kolbam.ⁱⁱⁱⁱⁱⁱⁱ Although Kolbam was approved for different therapeutic indications, the SmPC and in the assessment report of Kolbam noted that Kolbam was also effective in the treatment of the therapeutic indications for which Orphacol was already authorised and had obtained the market exclusivity. Laboratoires CTRS considered that a reference to the efficacy for the Orphacol indications constituted a circumvention of the market exclusivity of Orphacol and requested, in essence, for an annulment of the marketing authorisation of Kolbam in so far as it referred to the Orphacol therapeutic indications.^{mmmmmmmm}

Arguments of the parties

First the European Commission raised questions on the admissibility of the claims of Laboratoires CTRS in regard to the contested statements in the SmPC and assessment

ⁱⁱⁱⁱⁱⁱⁱ i.e. Off-label use.

^{jjjjjjj} *T-452/14 Laboratoires CTRS v Commission* [2015].

^{kkkkkkkk} Art. 8 Regulation (EC) No 141/2000.

ⁱⁱⁱⁱⁱⁱⁱ *T-452/14 Laboratoires CTRS v Commission* [2015], paragraph 20.

^{mmmmmmmm} *T-452/14 Laboratoires CTRS v Commission* [2015], paragraph 43.



report.ⁿⁿⁿⁿⁿⁿⁿⁿ On the content of the case Laboratoires CTRS alleged an infringement of Article 8(1) of Regulation No 141/2000. It maintained, in essence, that the contested decision would undermine the 10-year period of market exclusivity from which Orphacol benefited on the basis of that provision.^{oooooooo} Laboratoires CTRS also submitted that *“such circumvention of the market exclusivity attaching to Orphacol also results from the fact that the presence in the SmPC and the assessment report of statements concerning the efficacy of Kolbam for the Orphacol therapeutic indications could lead doctors to prescribe Kolbam for therapeutic indications other than those for which it has been authorised.”*^{pppppppp}

On the contrary Commission argued that *“since, formally, the marketing authorisation for Kolbam was not granted for the Orphacol therapeutic indications, there can be no breach of Orphacol’s market exclusivity for those therapeutic indications. Similarly, the intervener submits that only the therapeutic indications mentioned in section 4.1 of the SmPC are covered by the marketing authorisation in question and that, since the information in section 5.1 of the SmPC cannot be understood as an authorisation for the medical conditions mentioned therein, there can be no breach of market exclusivity.”*^{qqqqqqqq}

Ruling (factual outcome)

First the court dealt with the admissibility of the claims of Laboratoires CTRS in regard to the contested statements in the SmPC and assessment report. The court reasoned that the content of the SmPC and that of the assessment report are an integral part of the statement of reasons for the contested decision of the Commission. Accordingly, the SmPC and the assessment report must be examined in the context of the application for annulment of the contested decision to grant a marketing authorisation.^{rrrrrrrr}

Subsequently, the General Court considered the content of the case, including the effect of off-label prescribing on the market exclusivity. It alleged that *“off-label prescribing of a medicinal product for therapeutic indications covered by the market exclusivity attaching to another medicinal product (...) should not be facilitated”*^{ssssssss} in order to ensure the effectiveness of market exclusivity.^{ttttttt} The court deemed that this was even more important since EU law does not regulate off-label use.^{uuuuuuuu}

“Such a consideration is particularly compelling given that off-label prescribing is not prohibited, or even regulated, by EU law. There is no provision which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted.”^{vvvvvvvv}

To state that a medicinal product is effective for the treatment of therapeutic indications under market exclusivity of another medicinal product would amount to circumvention of the market exclusivity.^{wwwwwww}

ⁿⁿⁿⁿⁿⁿⁿⁿ T-452/14 Laboratoires CTRS v Commission [2015], paragraph 45-65.

^{oooooooo} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 66 and 69.

^{pppppppp} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 74.

^{qqqqqqqq} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 67.

^{rrrrrrrr} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 62.

^{ssssssss} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 78.

^{ttttttt} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 78.

^{uuuuuuuu} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 79.

^{vvvvvvvv} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 79.

^{wwwwwww} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 81.



Furthermore, "off-label prescribing is the sole responsibility of the prescribing physician".^{xxxxxxx} Reference to off-label therapeutic indications in the product information could attenuate that responsibility.^{yyyyyyy} In addition, the General Court reasoned that the EU regulations on advertising for medicinal products do not preclude promotional statements about the efficacy of Kolbam for Orphacol therapeutic indications.^{zzzzzzz} Moreover, physicians also use the SmPC as a source of information.^{aaaaaaa} In the end, the court concluded that the contested references in the SmPC and the assessment report of Kolbam were liable to facilitate off-label prescribing of Kolbam, which gave rise to the circumvention of the market exclusivity of Orphacol.^{bbbbbbb}

Subsequently, whereas the commission repeatedly attempted to justify the presentation in the SmPC and the assessment report of the clinical studies submitted by the marketing authorisation holder of Kolbam regarding the therapeutic indications of Orphacol, the court recalled that the Laboratoires CTRS did not challenge the presentation of such studies, while the arguments of the Commission did not establish the need to include in the SmPC and assessment report a conclusion concerning the efficacy of Kolbam for the therapeutic indication of Orphacol. In the end, the court annulled Commission decision granting the marketing authorisation for Kolbam

After all, it should be understood that off-label use of medicinal products is not prohibited by EU legislation, since it has not been regulated. Nevertheless, off-label therapeutic indication may, at least, not be referred to in the SmPC and assessment report as far as it concerns therapeutic indications of a medicinal product under market exclusivity.

The Netherlands

Case Netherlands Society of Cardiology v Dutch Government – Judgement of the Court of appeal The Hague of 20 April 2006

Issue(s) at stake

The case concerned an appeal in a preliminary relief proceeding in which the Netherlands Society of Cardiology demanded the reimbursement of Plavix (clopidogrel) for an off-label use, i.e. the use after placement of an elective stent placement, after the Dutch Minister of Health decided to limit the reimbursement.

Factual Background

The Dutch advisory board of pharmaceutical care (Commissie Farmaceutische Hulp) had advised the Dutch minister of Health not to reimburse Plavix for the uses proposed by the Society since it had no clear additional therapeutic value over existing treatment options. The court of The Hague rejected the claim of 6 January 2006.^{ccccccc} The Netherlands Society of Cardiology filed an appeal. The Dutch court of appeal of

^{xxxxxxx} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 82.

^{yyyyyyy} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 82.

^{zzzzzzz} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 84 to 88.

^{aaaaaaa} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 92 to 95.

^{bbbbbbb} T-452/14 Laboratoires CTRS v Commission [2015], paragraph 97.

^{ccccccc} Court of The Hague, 6th January 2006, ECLI:NL:RBSGR:2006:AU9166 (ruling in preliminary relief proceedings).



The Hague issued their verdict on 20 April 2006.^{ddddddddd} The following assessment primarily concerns the appeal procedure.

Arguments of the parties

The Netherlands Society of Cardiology argued that the reimbursement of Plavix after placement of an elective stent placement was in line with national and international clinical practice. The society reasoned that the lack of reimbursement would impede optimal treatment, because the lack of reimbursement caused a substantial share of their patient to refrain from the use of Plavix. This would also harm the relationship between patients and their physician. Moreover, the Dutch State would violate the professional autonomy of the cardiologists, because cardiologists could not treat their patient in accordance with medical guidelines. The arguments of the Dutch Government are not described explicitly in the judgment.

Ruling (factual outcome)

The Court reasoned that the Dutch Minister of Health did not act contrary to the law with its decision not to reimburse Plavix for the proposed therapeutic indication. The Minister has a board margin of discretion in the assessment for reimbursement of medicinal products. Except from urgent reasons the minister will only place products on the reimbursement list for their licensed uses.

Moreover, the court ruled that the decision not to reimburse Plavix is not contrary to the physicians' legal obligation to exercise the level of care expected from a conscientious health care provider and therefore to comply with professional guidelines. The lack of reimbursement does not prevent the physician to prescribe the medicinal product for the off-label use although he has to explain to the patient that the medicinal product is for the patient's own expenses. The latter would actually be part of the physician's legal obligation.

The court established that it would not rule on the actual additional benefit of the use of Plavix after stent placement. Parties disagree on this matter and the court could not rule on this matter without further furnishing of proof, while this cannot be part of an appeal case for appeal for a preliminary relief.

An assessment of the interest of the cardiologists not to pressurize the patient-physician relationship and the interest of the government for cost containment would only result in disregarding the decision not to reimburse Plavix if the decision would be evidently unlawful, which it is not in the present case according to the court.

Case Parents v health care insurance company regarding reimbursement of bosentan – Judgement of the Dutch Supreme court of 19 December 2014

Issue(s) at stake

The present case concerned a ruling of the Dutch Supreme court on the reimbursement of off-label use of bosentan used off-label.

Factual background

An eleven-year-old girl suffers from *limited scleroderma* a chronic systemic autoimmune disease characterized by hardening of the skin with cutaneous manifestations that mainly affect the hands, arms and face. The girl cannot be treated satisfactory and therefore she is prescribed bosentan. Bosentan has been authorized for the treatment of *limited scleroderma in adults*. For children bosentan has only been authorized for other therapeutic indications. Consequently, the reimbursement of

^{ddddddddd} Court of appeal The Hague 20th April 2006, ECLI:NL:GHSGR:2006:AW2484 (ruling in the appeal case).



bosentan in the treatment of *limited scleroderma* had been limited to the treatment of adults.

In a preliminary relief proceeding the court ruled that the health insurance company had to reimburse the use of bosentan. This judgement was based on Dutch case-law on reimbursement prior to the review of the reimbursement system in 2006 from a partly governmental organized reimbursement system to a fully privately organized reimbursement system. The court inferred a hardship clause for the reimbursement under exceptional circumstances from case-law prior to 2006. This hardship clause was based general principles of good governance. The court in first instance established a similar exception from the civil principles of reasonableness and fairness under the new reimbursement legislation.^{eeeeeeee}

Arguments of the parties

The health insurance company opposed the principle of reasonableness and fairness as basis for reimbursement and the reasoning of the court regarding the existence exceptional circumstance. Parties agree to directly refer the case to the Dutch supreme court, which had to determine to what extent under the new privately oriented reimbursement system an exception could be established on the principle of reasonableness and fairness.^{ffffff}

Ruling (factual outcome)

The supreme court reasoned that based on the principle of reasonableness and fairness an exception can (and should) be made in case of exceptional circumstances and which have not been considered by the government in its assessment on the reimbursement. In those circumstance a medicinal product may be reimbursed if i) the cost are so high that the insured cannot afford it himself, ii) there is no alternative treatment, iii) the medicinal product is necessary because of a serious medical condition that is life threatening or cause serious suffering, and iv) it may be assumed that the medicinal product partly of its efficacy, necessity and efficiency, is eligible for or will be included on the reimbursement list. The court assessed the circumstances the present case and confirms the judgment of the court in first instance.

Case Zilveren Kruis v Apotheek Ridderveld – Judgment of the Court of appeal The Hague of 3 March 2015

Issue(s) at stake

The present case concerned an appeal case about the reimbursement and wrongful declaration of the costs of infliximab in the treatment of severe therapy resistant hidradenitis suppurativa and severe therapy resistant sarcoidosis.

Factual Background

The parties are Zilveren Kruis Achmea Zorgverzekeringen N.V. in concert with others ("Zilveren Kruis") v. Apotheek Ridderveld B.V., Sprint Holding B.V., White Dolphin Farma B.V., ("Apotheek Ridderveld"). Apotheek Ridderveld had supplied infliximab to their patients and had claimed the expenses at the health care insurance company Zilveren Kruis. The latter who initially reimbursed the cost later wanted to recover the amount, because the reimbursement was not in accordance with additional

^{eeeeeeee} Court of Gelderland 19th July 2013, ECLI:NL:RBGEL:2013:3104 (ruling in preliminary relief proceedings).

^{ffffff} Supreme court 19th December 2014, ECLI:NL:HR:2014:3679 (leap-frogging appeal to the Supreme Court).



requirements for reimbursement set out in the Dutch Health insurance law and related regulations (i.e. Bijlage 2 Regeling zorgverzekering).

Zilveren Kruis required that for therapy resistant hidradenitis suppurativa the patient first should have been treated with systemic immunosuppressive drug and antibiotic without success. For therapy resistant sarcoidosis the patient should first be treated with two immunosuppressive drugs without success. In the case in first instance the court had ruled in favour of Zilveren Kruis.^{gggggggggg} The main question in the appeal is whether the requirements established by Zilveren Kruis are in accordance with the requirements in the Dutch health insurance law (i.e. Bijlage 2 Regeling Zorgverzekering) as determined by the Dutch advisory board of pharmaceutical care (Commissie Farmaceutische Hulp).^{hhhhhhhh}

Arguments of the parties

In short Zilveren Kruis argued that the requirements it established to the reimbursement of infliximab are only an administrative translation of the requirements established by the government.

Apotheek Ridderveld on the contrary argued, in short, that the treatment requirements established by Zilveren Kruis are no part of standard therapy and cannot be inferred from the reports of the Dutch advisory board of pharmaceutical care.

Ruling (factual outcome)

In regard to the treatment of therapy resistant sarcoidosis the court ruled that the policy of Zilveren Kruis is appropriate, although there may be exceptional circumstances in which treatment with two immunosuppressive drugs would not be required. However, such exceptional circumstances should have been further substantiated by Apotheek Ridderveld which has not been done in the present case.

In regard to therapy resistant hidradenitis suppurativa the court concludes that there may be doubts on the assessment by the Dutch advisory board of pharmaceutical care. It doubts whether the board had meant that therapy resistant hidradenitis suppurativa only existed after unsuccessful treatment both an antibiotic and immunosuppressive drugs, as was established by Zilveren Kruis as an requirement for reimbursement of infliximab. The court required to provide additional proof to substantiate their claim.

In a subsequent ruling the court concludes that Zilveren Kruis did not substantiate that its interpretation of Zilveren Kruis is supported by the evaluation of the Dutch advisory board of pharmaceutical care that established the legal terms for the reimbursement of infliximab, since their evaluation may be understood as that treatment with immunosuppressive drugs would only be appropriate in specific circumstances.ⁱⁱⁱⁱⁱⁱⁱⁱ

Note: since the 1st of January 2012 infliximab has been designated as inpatient-care and needs to be paid for by hospitals. Therefore, the practice in the present case has become obsolete.

^{gggggggggg} Court of The Hague 5th June 2013, ECLI:NL:RBDHA:2013:CA2375 (ruling in first instance).

^{hhhhhhhh} Court of appeal The Hague 3rd March 2015, ECLI:NL:GHDHA:2015:342 (interlocutory ruling in the appeal case).

ⁱⁱⁱⁱⁱⁱⁱⁱ Court of appeal The Hague 29th December 2015, ECLI:NL:GHDHA:2015:3565 (final judgment in the appeal case).



Annex D Summary of EU court cases

Case	Legislation and article(s)	Content/tenor of Article(s)	Court case issue	Relevance to off-label
T-13/99 <i>Pfizer Animal Health</i>	Treaty on the Functioning of the European Union Article 191	The precautionary principle enables rapid response in the face of a possible danger to human, animal or plant health, or to protect the environment. In particular, where scientific data do not permit a complete evaluation of the risk, recourse to this principle may, for example, be used to stop distribution or order withdrawal from the market of products likely to be hazardous. Where there is scientific uncertainty as to the existence or extent of risks to human health, the Community institutions may, by reason of the precautionary principle, take protective measures without having to wait until the reality and seriousness of those risks become fully apparent .	The application of the precautionary principle by the European Union Community Institutions.	The ruling deals predominantly with the powers of the Union institutions under the precautionary principle. This principle is mainly relevant for cases where a risk has not yet been scientifically assessed. The regulation of medicinal products already contains mechanisms in respect of emerging risks and Union action in response (pharmacovigilance). The relevance of this ruling is for off-label use of medicines seems limited.
T-74/00 <i>Artegodan</i>	Directive 75/319 <i>Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products</i> Article 12 Article 15a	<u>Article 12:</u> The Member States or the Commission or the applicant or holder of the marketing authorisation may, in specific cases where the interests of the Community are involved, refer the matter to the Committee for the application of the procedure laid down in Article 13 before reaching a decision on a request for a marketing authorisation or on the suspension or withdrawal of an authorisation , or on any other variation to the terms of a marketing authorisation which appears necessary, in particular to take account of the information collected in accordance with Chapter Va. <u>Article 15a:</u> 1. Where a Member State considers that the variation of the terms of a marketing authorisation which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary for the protection of public health , the Member State concerned shall forthwith refer the matter to the Committee for the application of the procedures laid down in	The power of the European Commission to withdraw or suspend marketing authorisations granted on purely a national level.	The relevance of this ruling for off-label use of medicines is very limited. The ruling deals predominantly with the power of the Commission to withdraw national marketing authorisations on the level of the EU. The EU legislation has changed since then and currently the issue would be dealt with without legal concerns.



		Articles 13 and 14. 2. Without prejudice to the provisions of Article 12, in exceptional cases, where urgent action is essential to protect public health, until a definitive decision is adopted a Member State may suspend the marketing and the use of the medicinal product concerned on its territory. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action.		
C-62/09 <i>ABPI</i>	Directive 2001/83 Article 94(1)	Where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy.	The applicability of this Article to financial incentive schemes implemented by national public health authorities.	Financial incentive schemes implemented by the public authorities are subject to article 94(1) of Directive 2001/83/EC on promotion of medicinal products. The relevance of this ruling for off-label use of medicines is limited as the on-label or off-label nature of the promoted medicinal product is irrelevant.
C-179/16 <i>Hoffman-LaRoche</i>	Treaty on the Functioning of the European Union <i>Article 101 (ex Article 81 TEC)</i>	Article 101 of the Treaty on the Functioning of the European Union (TFEU) prohibits agreements between companies which prevent, restrict or distort competition in the EU and which may affect trade between Member States (anti-competitive agreements).	Are the agreements between the beneficiaries of Lucentis and Avastin compliant with EU competition legislation? Definition of the relevant market and considerations regarding interchangeability of the two products. <i>Request for preliminary ruling (referring Court: Italian Consiglio di Stato)</i>	Ruling is awaited.
C-249/09 <i>Novo Nordisk</i>	Directive 2001/83 Article 87(2)	All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics .	The applicability of this Article to quotations taken from medical journals or other scientific work.	Claims for off-label use, even well-documented, are not acceptable in advertising/promotion of an approved medicinal product.
C-185/10 <i>Commission v Poland</i>	Directive 2001/83 Article 5(1)	A Member State may, in accordance with legislation in force and to fulfil special needs , exclude from the provisions of this Directive	The interpretation of 'special need' and the scope of the exemption	The court established that the derogation from the need for a marketing authorisation



		medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility.	from the requirement for a marketing authorisation through named patient supply.	requirement through named patient supply should remain exceptional to preserve the practical effect of the marketing authorisation. It may only be exercised if necessary taken into account the specific needs of patients. The court did not comment on derogations from an already granted marketing authorisation, as is the case in off-label use.
C-535/11 <i>Novartis Pharma</i>	Regulation 726/2004 Article 3 (1)	No medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation.	The scope of the requirement for a marketing authorisation.	The relevance of this ruling for off-label use of a medicinal product is unclear, since the ruling deals with the need to obtain a marketing authorisation and any exemptions to this requirement.
T-452/14 <i>Laboratoires CTRS v European Commission</i>	Regulation 141/2000 Article 8 (1)	Where a marketing authorisation in respect of an orphan medicinal product is granted pursuant to Regulation (EEC) No 2309/93 or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition laid down in Articles 7 and 7a of Directive 65/65/EEC or Article 9(4) of Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (1), and without prejudice to intellectual property law or any other provision of Community law, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication , in respect of a similar medicinal product.	The lawfulness of information in the Summary of Product Characteristics, other than section 4.1, on the effectiveness of the product in therapeutic indications covered by market exclusivity attached to another medicinal product.	Off-label prescribing is not prohibited, or even regulated, by EU law. An off-label therapeutic indication may not be referred to in the Summary of Product Characteristics and the Assessment Report as far as it concerns therapeutic indications of a medicinal product under market exclusivity.



Annex E Prevalence studies, children

MS	Medicinal product(s)	Therapeutic area(s)	Off-label aspect(s)	Target group	Setting	Number	Frequency off-label	First author and Year of publication
Inside hospital (bold figures are presented in figure 3.1)								
FR	Psychotropic medications: anxiolytics, antipsychotics, antidepressants, antiepileptics, stimulants, antiparkinsonians and hypnotics. The 5 drugs most commonly prescribed off-label were risperidone, clobazam, amitriptyline, hydroxyzine and diazepam.		Indication, dosing, contra-indication, and target population	0-18 years	Hospital-inpatient	472 patients and 1629 drug prescriptions	68% of all prescriptions were off-label. Per age group: neonates 91%; adolescents 74%; children 59% and infants 58%. 66% of patients received off-label medications. ⁶⁴	Winterfeld 2009
FR	Psychotropic medication	Psychiatry	Indication, target population, dosing, contra-indication, and administration route	5-17 years	Hospital-inpatient	187; 421 prescriptions	69% of all prescriptions. Per medication class: antipsychotic drugs 90%, anxiolytics 28%, stimulants 26%, antidepressants 89%, antiepileptics 89%, antiparkinsonian drugs 91%. ⁶⁵	Winterfeld 2008
AT	Various medicines (a.o. fentanyl, theophyllin, midazolam, vancomycin, chloralhydrate)	A.o. cardiology, respiratory system drug, central nervous system drugs, anti-infectives	Indication, target population, dosing	Prematures and children < 1 month	Hospital-inpatient	748 prescriptions	33% ⁶⁶	Prandstetter 2009
BE	Three most common medicines prescribed off-label: paracetamol i.v., dopamine, salbutamol.	Paediatrics	Indication, target population, dosing, formulation, administration route	0-18 years	Hospital-inpatient	1109; 5555 prescriptions	General paediatrics: 43,5%; paediatric Intensive Medium Care Unit: 51,2%; NICU: 54,2%; Total: 49,7% ⁶⁷	Annicq 2008
DE	Various medicines	Paediatrics	Indication, dosing, target population and administration route	0-18 years	Hospital-inpatient	1812 prescriptions	31% (60% of all cardiovascular drugs; 42% of all anti-infectives; 30% of all respiratory system drugs; 25% of all alimentary tract and metabolism drugs; 3% of all analgesics) ⁶⁸	Hsien 2008



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EE	Various medicines (cardiovascular drugs, anti-infectives, respiratory system drugs, alimentary tract and metabolism drugs, central nervous system)	Various areas within neonatology	Target population, contra-indication, special warnings	Prematures and children < 1 month	Hospital-inpatient	1981 prescriptions	65% (<28 weeks: 62%; 28-31 weeks: 68%; 32-36 weeks: 80%; full term: 57%) ⁶⁹	Lass 2011
ES	Various medicines (a.o. ibuprofen, paracetamol, salbutamol, amoxicillin)	Various areas (anti-infectives, respiratory system drugs, alimentary tract and metabolism drugs, central nervous system, musculoskeletal system group)	Indication, dosing, target population, and administration route	0-13 years	Hospital-inpatient	667 prescriptions	51% (24.3% lack of information; 32.7% indication; 4,7% target population; 38.1% dosing) ⁴⁰	Morales-Carpi 2010
ES	Intravenous human immunoglobulin	various areas (a.o. neurology, hematology, pneumology)	Indication	Children and adolescents (15.7%) and adults (84.3%)	Hospital-inpatient	1287 prescriptions	26% (11% accepted indication and 15% non-accepted) ³¹	Ruiz-Antoras 2010
FI	Various medicines (anti-infectives, analgesic/antipyretic agents, respiratory system drugs, central nervous system, alimentary tract and metabolism drugs)	Various areas	Indication, dosing, contra-indication, target population, special warnings and administration route	0-18 years	Hospital-inpatient	1054 prescriptions	42% (0-27 dagen: 51%; 28d-23 months: 42%; 2-11 years: 38%; 12-18 years: 35%) (41% dosing; 24% target population; 21% administration route; 16% contra-indication; 16% indication) (most commonly prescribed for off-label use: fentanyl, paracetamol, salbutamol, midazolam) ⁷⁰	Lindell-Osuagulu 2014
FI	Various medicines (anti-infectives, analgesic/antipyretic agents, respiratory system drugs, central nervous system, alimentary tract and metabolism drugs)	Various areas	Indication, dosing, contra-indication, target population, special warnings and administration route	0-18 years	Hospital-inpatient	629 prescriptions	36% (0-27 dagen: 7%; 28d-23 months: 34%; 2-11 years: 45%; 12-18 years: 14%) (22% dosing; 50% target population; 34% administration route; 2% formulation; 19% indication) ¹⁵	Lindell-Osuagulu 2009
FR	Psychotropic medicines (e.g. cyamemazine, risperidone, methylphenidate)	Psychiatry	Indication, target population, dosing, contra-indication, administration route	2-15 years old	Hospital-inpatient	295 prescriptions	25% off-label ⁷¹	Serreau 2004



OFF-LABEL

FR	Various medicines (e.g. caffeine, domperidon, dopamine, midazolam, dobutamine, dexamethasone, ketamine)	Various areas	Indication, dose, administration route	Neonates 0-128 days old; preterm and term	Hospital-inpatient	257 prescriptions	62% (90% for age; 9.3% for dose; 0.7% for administration route) ¹⁸	Avanel 2000
IE	Various medicines (gentamycin, benzylpenicillin, morphine sulphate, chlorhexidin 2% solution, cyclopentolate)	Various areas within neonatology	Indication, dosing, target population and administration route	Prematures and children < 1 month	Hospital-inpatient	69 prescribed drugs	39% (infants <32 week gestation: 94% received an off-label drug; all infants < 28 week gestation off-label) ¹⁴	Kieran 2013
IT	Various medicines (a.o. salbutamol, beclomethasone, betametasone, paracetamol, ceftriaxone, hydrocortisone/neomycin/naphazoline, clarithromycin, adrenalin, droperidol)	Various areas (a.o. respiratory disease, analgetics/anti-pyretics, infectious disease, cardiovascular disease)	Indication, dosing, target population, formulation and administration route	0-14 years	Hospital-inpatient	4265 prescriptions	60% (of which: 60% dosing, 11% indication, 19% target population; 6% administration route; 4% formulation) (antibacterials: 52%; anti-asthmatics: 60%; analgetics/antipyretics: 59%; corticosteroids: 55%; psycholeptics: 66%; antacids: 86%; anti-diarrhoeals: 63%; cough/cold: 54%) ⁷²	Pandolfini 2002
IT	Antiemetic drugs (metoclopramide, ondansetron, granisetron)	Antiemetic drugs	Indication, dosing, administration route	0-18 years	Hospital-inpatient	19,879 doses	30% (of which: 10% for indication and 20% for target population) ⁷³	Zanon 2013
IT	Various medicines	Various areas within neonatology	Indication, dosing and administration route	Children < 1 month	Hospital-inpatient	88 prescriptions	47.7% ; Among antibiotics 56.8% of usage was off-label. Other drugs, ranitidine was used off-label as the intravenous route of administration was chosen, while in the other cases the off-label use regarded the administration of acetylsalicylic acid, paracetamol, furosemide, corticosteroids and bronchodilators without any indication in the newborn despite the fact that in some cases there is a large experience of use in newborns and infants ⁷⁴	Dessi 2010
IT	Various medicines	Various areas within neonatology	Indication, dosing, contra-indication, special warnings and	Prematures and children < 1 month	Hospital-inpatient	176 prescriptions	27.8% (of which: 45% dosage, mainly systemic antibiotics.); 22.7% contained no information on paediatric use in SmPC ¹¹	Dell'Area 2007



OFF-LABEL

			administration route					
IT	Various medicines (furosemide, phenobarbital, theophylline/aminophylline, ranitidine, calcium gluconate, sodiumbicarbonate)	Various areas within neonatology	Indication, dosing, target population and administration route	Prematures and children < 1 month	Hospital-inpatient	483 prescriptions	46.5% (44.4% preterm; 50.7% full term) ⁷⁵	Laforgia 2014
KR	Various medicines (a.o. pantoprazole, esomeprazole, ranitidine, granisetron, oxymetazoline)	Various areas (Neonatology/intermediate care, intensive care, neurology, nephrology, hematology/oncology, endocrinology, cardiology/pulmonology)	Indication, dosing, contra-indication, target population	0-19 years	Hospital-inpatient	1643 prescriptions	13.5% (Neonatology/intermediate care: 15.5%; ICU: 19.7%; Neurology 12.4%; Nephrology: 10.4%; Hematology/oncology: 14.6%; Endocrinology 6.0%; Cardiology/pulmonology: 5.6%) (0-28 days: 23.8%; 29 days-1 year: 16.9%; 1-2 years: 14.6%; 3-6 years: 20.5%; 7-11 years: 10.2%; 12-18 years: 3.9%) ⁷⁶	Palcerski 2012
NL	Various medicines (a.o. Paracetamol, Cefotaxime, Amoxicillin, Cisapride, Salbutamol, Budesonide)	Various areas (respiratory system, analgesic/anti-pyretics, anti-infectives, alimentary tract and metabolism drugs)	Indication, dosing, target population, dosage form, administration route, contra-indication	0-17 years	Hospital-inpatient	1017 prescriptions	43.6% (of which: dosing 24.4%, target population 15.4%, indication 2.5%, contra-indication 0.5%, dosage form 0.3%, administration route 0.1%) ⁷⁷	't Jong 2002
NL	various medicines (a.o. ciprofloxacin, cisapride, paracetamol, ondansetron)	Various areas (a.o. Cardiovascular drug, respiratory system drugs, analgesics/anti-pyretics, anti-infectives, alimentary tract and metabolism drugs)	Indication, dosing, target population, dosage form, administration route, contra-indication	0-17 years	Hospital-inpatient	2139 prescriptions	18% ⁷⁸	't Jong 2001
NL	Various oncological medicines (a.o. Cytarabin, Etoposide, Carboplatin, Doxorubicine, intrathecal prednisolone)	Paediatric oncology	Indication, dosing, target population, dosage form, administration route, contra-indication	children ≤ 17 years	Hospital-inpatient	268 prescriptions	43% ²⁶	Van den Berg 2011
PT	Various medicines (a.o. Amoxicillin/clavulanic acid, paracetamol, amoxicillin, ibuprofen and salbutamol)	Various areas (a.o. respiratory disease, analgesics/anti-pyretics, infectious disease, central nervous system,	Indication, dosing, target population, administration route	0-18 years	Hospital-inpatient	724 prescriptions	32.2% ¹⁹	Ribeiro 2013



OFF-LABEL

		musculoskeletal drugs)						
PT	All active substances (n=84) prescribed to neonates in this hospital. By order of frequency: anti-infectives, nervous system, alimentary tract, cardiovascular system, blood forming organs.	Multiple, depending on the drug. By order of frequency: anti-infectives, nervous system, alimentary tract, cardiovascular system, blood forming organs.	Indication Contra-indication Dosing Target population/age Administration route	Children < 1 month	Hospital-inpatient	A total of 1011 prescriptions	Total: 52,7% off-label prescriptions (47% in preterm, 60.9% in full-term). By type of off-label use: -Dose and/or frequency: 25.7% of the cases. -Gestational age and dose simultaneously: 1.4%. -Age: 10.1% -Contra-indication: 8.7% ²³	Silva 2015
SE	Various medicines	Various areas	Indication, dosing, contra-indication, weight, target population, special warnings and administration route	0-18 years	Hospital-inpatient	11294 prescriptions	34% (57% 0-28 days old; 48% >28 months to 24 months; 41% 2-<12 years; 28% 12<18 years) (Among the most common authorized substances used off-label were carbohydrates, electrolytes, paracetamol, sodium chloride, diclofenac, sulfamethoxazole/trimethoprim, morphine, midazolam, epinephrine, heparine) ⁷⁹	Kimland, 2012
UK	The commonest drugs were: terbutaline, ipratropium bromide, ranitidine, paracetamol, senna, salmeterol, cephalixin, multivitamin drops.	Various areas within paediatrics	Mainly dose but also age and indication	1 wk - 13 years	Hospital-inpatient	74 patients, 237 drug prescriptions	19,4% of prescriptions were off-label ⁸⁰	Craig, 2001
UK	Psychotropic medicines (e.g. Antipsychotics, antidepressants, hypnotics, antiepileptics as mood stabilisers; risperidone, olanzapine, clozapine, valproate)	Psychiatry	Indication, target population, dosing	adolescents and adults up to 25 years old; 14-21 years	Hospital-inpatient	89 patients; 202 prescriptions	78.7% patients; 67.8% prescriptions ⁸¹	Haw, 2010
UK	Analgesic agents	Central nervous system	Indication, dosing, target population, weight and administration route	children (age range not indicated)	Hospital-inpatient	715 prescriptions	33% (12% dose; 7% administration route; 7% target population; 7% indication; 1% weight) ²¹	Convoy, 2001



OFF-LABEL

UK, IT, EL	Antibacterial agents	Infectious disease	Indication, dosing, target population, administration route	0-17 years	Hospital-inpatient	1244 prescriptions	NICU: Dosing: 37.8% UK, 51.7 IT, 44.4% EL; Indication: 23.3% UK, 38,5% IT, 25,5% EL. Paediatric ward: Dosing: 29.9% UK, 27.5% IT, 25.3% EL; Indication: 28.4% UK, 30.0% IT, 19.7% EL. ⁴¹	Porta, 2010
UK, SE, DE, IT, NL	Various medicines	Various areas	Indication, dosing, target population, formulation and administration route	0-16 years	Hospital-inpatient	2262 prescriptions (798 UK; 185 SE; 224 DE; 398 IT; 657 NL)	39% (UK: 23% ; SE: 26% ; DE: 37% ; IT: 66% ; NL: 45%) ¹⁰	Conroy, 2000
DK	Leuproreline, metopimazine, golimumab, ciclosporin, posaconazole, colchicine, amphotericin B, melatonin, pegfilgrastim, estradiol, testosterone, dalteparin, tinzaparin	Various areas: neonatology and paediatric wards	Indication, target population, contra-indication and administration route	Preterm neonates < 36 up to children < 17 years	Hospital-inpatient	100 prescribed drugs	13% ³²	Hasland Krag 2014
UK	Various medicines	Gastro-enterology	Indication, target population, dosing and administration route	Children 20 days to 17 years	Hospital-inpatient	777 prescriptions	37,4% (of which: 71.5% indication, 28.5% target population) ¹²	Dick, 2003
Outside hospital (bold figures are presented in figure 3.2)								
NL	Various medicines	Central nervous system, respiratory system, alimentary tract and metabolism.	Indication Target population	4-18 years	Schools and facilities for children and adolescents with mental retardation	912 children	Nervous system: 34% Respiratory system: 27% Alimentary tract and metabolism: 27% ⁸²	Tobi, 2005
CZ	Various medicines (a.o. salbutamol, desloratadine, mometasone, cetirizine, clarithromycin, fluticasone furoate)	Various areas	Indication, target population	0-15 years	Hospital-outpatient	8559 prescriptions	9.0% The five drug groups most frequently prescribed off-label were: cardiovascular drugs (60% of prescriptions), anti-infectives (42%), drugs of the respiratory system (30%), drugs of the alimentary tract and metabolism (25%) and analgesics and antipyretics (3%). The cardiovascular drugs also exhibited the highest number of drugs prescribed off-label due to the patient's age. ⁸³	Langerova, 2014



OFF-LABEL

DE	Various medicines (a.o. cardiovascular drugs, ophthalmologics/otologicals, dermatologicals, antiepileptics, antipsychotics, antidepressants, hypnotics/sedatives, analgesics/antipyretics)	various areas (a.o. Cardiovascular drugs, alimentary tract and metabolism drugs, central nervous system, dermatology, ophthalmology/otology, musculoskeletal system, urogenital system)	Indication, target population, dosing, administration route	0-16 years	Hospital-outpatient	1.59 million prescriptions	13.2% (of which: 75% target population); 78.6% eyes and ears; 57.9% dermatological; 55.2% cardiology; 45.2% musculoskeletal; 48.5% urogenital; 36.6% antidepressants ⁸⁴	Bucheler, 2002a
ES	Anti-acid (100% off-label use), anti-H ₂ (78.2%), proton pump inhibitors (58.0%), antibiotics (16.4%), and laxatives (14.3%). Some therapeutic groups (immunosuppressive agents, antiemetics), had extremely infrequent use (<5 prescriptions), but were used as off-label in all of the cases	Paediatric gastroenterology	Target population Dose	Children, mean age 6,1 years. 3 age groups: infants (<2 years), children (2-10 years), and adolescents (>11 years)	Hospital-outpatient	207 patients (and 331 drug prescriptions)	47.3% of patients AND 33,2% of prescriptions ⁸⁵	Ruiz-Antoran, 2013
KR	Antidepressants (a.o. amitriptyline; fluoxetine, citalopram, sertraline and fluvoxamine; tianeptine, mirtazapine; benzodiazepines)	Psychiatry	Indication, target population	8-18 years	Hospital-outpatient	139 patients	85.6% of patients ⁸⁶	Marsanic, 2012
DE	Various antidepressants	Central nervous system; antidepressants	Indication, target population	0-17 years	Hospital-outpatient, primary care	26,543 prescriptions	49.1% (40.2% target population, 16.6% indication, 7.7% both) ³⁰	Dorks, 2013
FR	Various medicines	Various areas	Indication, dosing, target population and administration route	0-15 years	Other	2522 prescriptions	29% (of which: 65% target population, 23% indication, 10% dosing, 7% administration route; 6% for more than 1 reason) (of which: 70% in neonates 0-27 days, 27% in 28 days to 23 months, 31% in 2-11 years, 36% in 12-17 years); 94% of prescriptions for eye drops and 100% of those for antibiotic eye drops were off-label. ²⁸	Chalumeau, 2000
NL	Systemic antibiotics	Infectious disease	Dosing	Children < 2-23 months	Other	30 730	3.9% ⁸⁷	De Jong, 2009
DE	Various medicines	Various areas	Indication, dosing and	0-16 years	Primary care	1.592.006 prescriptions	13.2% ³⁷	Bucheler, 2002b



OFF-LABEL

			formulation					
DE	Various medicines within the top 20 of each therapeutic area	Oncology, central nervous system, cardiology, infectious disease, lung disease	Contra-indication	0-18 years	Primary care	31.377.388 prescriptions	Oncology: 34% , Cardiology: 28%, Central nervous system: 10%, Lung disease: 7,5%, Infectious disease: 0% of the top 20 medicines; 23% of all drug substances ⁸⁸	Afentaki, 2014
FI	Triptanes, used for migraine	Central nervous system; analgesics	Target population	6-17 years	Primary care	2618 users	72% of all users (children 6-17 years); 69% (children 12-17 years) ¹⁷	Lindkvist, 2011
FR	Nasal decongestants (tixocortol, a corticosteroid, and tuaminoheptane, a sympathomimetic), H1 antihistamines (mequitazine, a phenothiazine derivative, and desloratadine), and corticosteroids (betamethasone and prednisolone) were the most frequently involved in off-label prescribing for indication.	paediatrics	Indication Dose Target group Administration route Contraindication	0-16 years	Primary care	1960 patients	37,6% of patients. - unapproved indication 56.4% - lower dosage 26.5% - higher dosage 19.5% - age not labeled 7.2% - incorrect route of administration 3.5% - contraindication 0.3% ³⁸	Palmaro, 2015
FR	Various medicines (a.o. General anti-infectives for systemic use; Systemic hormonal preparations such as betamethasone	Various areas (a.o. infectious disease, respiratory system disease, alimentary tract and metabolism drugs)	Indication, contra-indication, dosing, administration route	0-16 years	Primary care	1419 patients	42.4% of all patients; 18.9% of all prescriptions (11.5% indication; 4.7% dosing; 1.1% age; 1.2% contra-indication, 0.4% administration route) ⁸⁹	Horen, 2002
IT	Various medicines (a.o. salbutamol, beclomethasone, ambroxol, flurbiprofen)	Various areas (a.o. respiratory disease, analgetics/anti-pyretics, infectious disease)	Indication, target population	0-12 years	Primary care	8476 prescriptions	17% ⁹⁰	Pandolfini, 2005
IT	Various respiratory medicines	Asthma, recurrent wheezing	Indication and dosing	1 month-14 years	Primary care	electronic medical records of about 130 000 paediatric patients ranging from 0 to 14 years of age; 195 633 prescriptions	23.9% Salbutamol; 19,5% salbutamol/flunisolide or beclomethasone; 26,2% beclomethasone, 25,3% flunisolide; 17,7% Ipratropium; 19,2% overall for age; The great majority of off-label uses is under the age of 2 years, irrespective of the active substance. 55.8% off-label for indication ⁹¹	Baiardi, 2009



OFF-LABEL

MT	Mainly systemic hormonal preparations excluding sex hormones and insulins, and the respiratory system.	paediatrics	Dosing, target population	1-14 years	Primary care	209 prescriptions	51.7% of prescriptions ⁹²	Ellul, 2014
NL	Various respiratory medicines (Salbutamol (inhaled, off-label for age and dose), fluticasone (inhaled, off-label for dose), terbutaline (inhaled, off-label for dose), and sodium cromoglycate (nasal spray, no information on use in children).)	Respiratory system	Indication, dosing, target population, dosage form	0-17 years	Primary care	5253 prescriptions	20.3% (Target population (7.3%), dose (7.8%), frequency (3.8%), indication (4.5%) or dosage form (1.1%)) ⁹³	't Jong, 2004
NL	Systemic anti-infective agents (e.g. antibacterial, antimycotic, antiviral, vaccines, immunoglobulins; e.g. amoxicillin, azithromycin, trimethoprim, sulphamethoxazole/trimethoprim, erythromycin)	Infectious disease	Dosing, target population, indication, administration route	0-17 years	Primary care	2855 prescriptions	14.4% ⁹⁴	't Jong, 2002
NL	Antidepressants (a.o. TCAs such as imipramine and amitriptyline; SSRIs, such as fluoxetine, citalopram, paroxetine, sertraline and fluvoxamine; Venlafaxine)	Central nervous system	Indication	children ≤ 18 years	Primary care	354 prescriptions (2001) and 255 prescriptions (2005)	52.6% for TCAs in 2001, 41% in 2005; 16.7% for SSRIs in 2001, 34.4% in 2005; 22.2% for Venlafaxine in 2001, 58.3% in 2005 ⁹⁵	Volkers, 2007
SE	Various medicines (e.g. Hydrocortisone, propylene glycol, hydrocortisone, chloramphenicol, fusidic acid)	Various areas (Dermatologicals, Otolitics and ophthalmologicals, Psycholeptics and psychoanaleptics, Analgesics, Rhinologicals, Antihistamines for systemic use)	formulation, administration route, target population	Children ≤ 16 years	Primary care	575,526 prescriptions	20.7% (77.8% dermatologicals, 73.6 Otolitics/ophthalmologicals, 31.4% psycholeptics/analeptics, 25.8% analgesics, 22.1% rhinologicals) ³³	Ufer, 2003
UK	Paracetamol	Various areas	Dosing	0-12 years	Primary care	4423 prescriptions	18% (11% underdose; 2.9% overdose; 15% no dosing information) (27% overdosing in children 1-3 months; 25% potential underdosing in children 6-12 years) ⁹⁶	Kazouini, 2011
UK	Various medicines (a.o. paracetamol, amoxicillin, beclomethasone, Salbutamol, chloramphenicol, benzylpenicillin)	Various areas	Target population, dosing, administration route	0-12 years	Primary care	3347 prescriptions	10.5% ¹⁶	McIntyre, 2000



OFF-LABEL

UK	Antiasthma medication: Anticholinergics, oral β 2-agonists, long-acting β 2-agonists, inhaled corticosteroids and combinations of long-acting β 2-agonists and inhaled corticosteroids.	Respiratory system: asthma	Dosing, target population	0-16 years	Primary care	17163	6,1% ⁹⁷	McCowan, 2007
UK	Retapamulin	Infective disease	Target population	0-9 months	Primary care	148 prescriptions	2% ⁹⁸	Mundy, 2014
UK	Formoterol	Pulmonology	Target population	3-17 years	Primary care	5777 children	4,5% ⁹⁹	Wilton 2002
UK	Antibiotics	Infectious disease	Dosing	Adolescents 15-18 years	Primary care	23 911	19.2% ⁴⁶	Ekins- Daukes, 2003
UK	Various medicines	Various areas	Indication, dosing, target population, formulation	children <16 years	Primary care	167,865 patients	26.1% (of which: 40-50% lower dose, 35% higher dose, 6-16% age, 5-10% formulation; depending on age group) (off-label: 24.4% 0-4 years; 27.9% 5-11 years; 26.0% 12-16 years); Antibiotics most frequently prescribed off-label: 26%, mostly due to lower dose. ¹³	Ekins- Daukes, 2004
UK	The 214 most frequently prescribed medicines -93,4% of all medicines prescribed- in primary care consultations for asthma)	Various areas (a.o. respiratory system/asthma)	Dosing, target population, and dosage form	Children aged 0-16 years	Primary care	unknown	The extent of off-label prescribing by participating general practice followed a normal distribution with an average of 24.6% and a range from 0 to 44%. ¹⁰⁰	Helms, 2005
UK, IT, NL	All prescribed drugs in children in primary care (top 5 off-label: topical inhaled and systemic steroids, oral contraceptives, and topical or systemic antifungal drugs)	Paediatrics: alimentary, blood, cardiovascular, dermatological, genitourinary, hormones, anti-infectives, antineoplastic, musculoskeletal, nervous system, antiparasitic, respiratory, sensory organs.	Target population	0-18 in NL and UK 0-14 in IT	Primary care	675.868 children	Too extensive to report here. All details are given on Table 4 (NL), Table 5 (UK), and Table 6 (IT) in the article. Highest percentage for one or more individual medicines was 100% in each of the three countries ¹⁰¹	Sturkenboom 2008



OFF-LABEL

UK, IT, NL	Respiratory drugs: - β 2-mimetics (short-acting [SABA] or long-acting [LABA]), - inhalation glucocorticosteroids, - inhalation anticholinergics, - fixed combination of SABA+short-acting anticholinergics, - fixed combination of LABA+inhalation glucocorticosteroids, - anti-allergic agents (best known as cromones), - xanthines, - leukotriene receptor antagonists.	Respiratory system	Indication and target population	0-18 years	Primary care	671,831 children of whom 49,442 had been diagnosed with asthma at any time during follow-up.	Target population: IT: - salbutamol for children <18 mo: 22.7/100 PY in children with asthma and 7.5 in children without asthma diagnosis. NL: - fixed combination β 2-mimetics + antichol. in children <6 years: 0.5-3.5/100 PY. Indication (in children without recorded asthma diagnosis): IT: budesonide had the highest off-label prescription rate (14.8/1000 PY); in NL: salbutamol (15/1000 PY); in UK: beclomethasone (11/1000 PY). Figures in figure 3.2 are calculated by MW and are: UK 74% , NL: 73% , IT: 80% ¹⁰²	Sen, 2011
IT	Various medicines	Various areas	Indication and contra-indication	0-18 years	Primary care and hospital-outpatient	4.027.119 dispensed drugs	3.3% (of which: 12.8% contra-indicated, 61.0% not recommended, 26.2% absence of paediatric information) ¹⁰³	Carnovale, 2013
DE	Analgesics, antibiotics, antidepressants	Various areas (a.o. central nervous system, infectious disease, analgesics)	Target population, dosing	0-18 years	Primary care, hospital outpatient	189,285 children and adolescents with analgesics-, 147,089 with antibiotics-, and 15,405 with antidepressant prescriptions	0.9% of patients using analgesics; 2.5% antibiotics; 8.5% antidepressants ¹⁰⁴	Sonntag, 2013
DE	Respiratory medicines (a.o. short-acting β 2-agonists (salbutamol, clenbuterol/ambroxol), long-acting β 2-agonists, short-acting muscarinic antagonists, long acting muscarinic antagonists, including fixed combinations; oral β 2-agonists)	Respiratory system	Target population, indication	0-18 years	Primary care, hospital-inpatient	487.899 prescriptions	29.8% ⁴⁴	Schmiedl, 2014



OFF-LABEL

NL	Various medicines (a.o. cardiovascular drugs, ophthalmologics/otologicals, dermatologicals, antimigraine preparations, antipsychotics, antidepressants, hypnotics/sedatives, anti-ulcer agents)	Various areas (a.o. Cardiovascular drugs, respiratory system drugs, alimentary tract and metabolism drugs, central nervous system, dermatology, ophthalmology/otology, musculoskeletal system, blood and blood forming organs)	Target population	0-16 years	Primary care, hospital-inpatient	66222 prescriptions	20.6% (18.9% 0-1 years; 16.4% 2-5 years; 18.8% 6-11 years; 27.4% 12-16 years) ¹⁰⁵	Schirm, 2003
DE	Various medicines (a.o. oral anti-diabetics, ulcer treatments, protonpump inhibitors, stomatological agents)	Various areas (alimentary tract and metabolism drugs, urogenital system and sex hormones, cardiovascular drugs, musculoskeletal system group)	Target population	0-16 years	Primary care, hospital-outpatient	1 429 981 prescriptions	3.2% ¹⁰⁶	Muhlbauer, 2009
EE	Various medicines (a.o. salbutamol, cetirizine, amoxycylav, diclofenac, chloramphenicol, mometasone, clarithromycin)	Various areas	Indication, dosing, contra-indication, special warnings, administration route	<19 years	Primary care, hospital-outpatient	467.334 prescriptions	31% (29% no paediatric information in SPC; 2% contra-indicated for age) The most commonly prescribed off-label products: respiratory system drugs and dermatologicals. ²⁰	Lass, 2011
SE	Various medicines (a.o. topically administered drugs, cardiovascular drugs, antidepressants, hypnotics and several NSAIDs)	Various areas (alimentary tract and metabolism drugs, urogenital system and sex hormones, cardiovascular drugs, musculoskeletal system group, dermatologicals, central nervous system)	Indication, dosing, contra-indication, target population, special warnings	0-18 years	Primary care, hospital-outpatient	2 177 859 prescriptions	13.5% (Genitourinary system & sex hormones 97.3%; dermatologicals 29.5%; cardiovascular 18.3%; CNS 12.8%; alimentary tract and metabolism 11.1% ¹⁰⁷	Olsson, 2011
SE	Medication indicated for asthma or COPD: short-acting β 2-adrenergics, long-acting β 2-adrenergics, inhaled corticosteroids, and fixed combinations of long-acting β 2-adrenergics and inhaled corticosteroids.	Asthma and COPD	Indication	All ages	Primary care	670 patients	150 individuals were prescribed off-label (this is 22% of the total population or 54% of the undiagnosed population) (15% in 0-17 years; 69% in 18-70 years; 17% > 70 years) ⁴⁸	Weidinger, 2014
DE	Psychotropic medication: antidepressants, antipsychotics, anxiolytics, and sedatives	Central nervous system	Indication Target population	0-17 years	Unknown	87 psychotropic medicines	37% (32/87) of all drugs: a) antipsychotics: 64% (16/25). b) antidepressants: 54% (7/13). c) sedatives: 75% (9/12). d) anxiolytics: 0% ¹⁰⁸	Koelch, 2009



Annex F Prevalence studies, adults

MS	Medicinal product(s)	Therapeutic area(s)	Off-label aspect(s)	Target group	Setting	Number	Frequency off-label	Year of publication
Inside hospital (bold figures are presented in figure 3.3)								
IT	Antineoplastic drugs	Oncology	Indication Other: used in association/alone in contrast with the approved use, or used with inappropriate timing	Not reported	Hospital-inpatient	644 patients receiving 1,053 drugs	18.9% of the prescriptions were off-label ⁵¹	Roila, 2009
BE	Intravenous human immunoglobulin	Surgery, oncology, orthopedics	Indication	unknown	Hospital-inpatient	9629 patients	46% ³⁹	Simoens, 2011
DE	Intravenous thrombolytic agents	Neurology	Contra-indication, target population	Adults	Hospital-inpatient	225 patients	55% ¹⁰⁹	Pawlik, 2012
DE	Tissue plasminogen activators	Cerebrovascular	Contra-indication	Adults 18->80 years	Hospital-inpatient	422 patients	55% ²²	Breuer, 2011
FR	Antibiotic Daptomycin	Anti-infectives	Indication	22-94 years old	Hospital-inpatient	21 patients	95% of prescriptions were off-label ⁴⁹	Marc, 2014
FR	Various medicines	Diabetology, neurology, pneumology, rheumatology, internal medicine, oncology	Indication, dosing, target population, contra-indication and administration route	Adults (age range not indicated)	Hospital-inpatient	1341 prescriptions	23% (of which: 75% indication, 14% dosage, 9% dosing schedule; 1% contra-indication, 1% administration route); 24% concerns anti-thrombotics, 17.7% anti-ulcer medicines, 6.6% anti-asthmatics, 6.3% vitamin supplements, 6.3% anti-epileptics, 4.9% corticosteroids, 34.2% other medicines. ³⁶	Cras, 2007
FR	Antibiotics, stress ulcer prophylactic drugs, vitamins, antiepileptic drugs were the main therapeutic classes used off-label.	Surgical intensive care unit	Indication, dosing, administration route	Adults 17-81 years	Hospital-inpatient	465 prescriptions	25.6% (of which: 66% indication, 27% dosing; 17% administration route) ²⁴	Albaladejo, 2001
FR	Various oncological medicines (a.o. docetaxel and oxaliplatin)	Oncology	Indication	Adults 18 years and older	Hospital-inpatient	1206 patients; 6168 chemotherapy cycles	6.7% of all prescriptions (57.6% in hormone-refractory prostate cancer; 37.6% bladder cancer) ¹¹⁰	Leveque, 2005



OFF-LABEL

FR	Psychotropic drugs (a.o. clonazepam, risperidone, divalproate, lamotrigine, oxcarbazepine, amisulpride, valpromide, oxazepam, hydroxyzine)	Psychiatry	Indication, dosing	Adults 18 years and older	Hospital-inpatient	261 prescriptions	39.8% of prescriptions (97% of anticonvulsants; 33% of mood stabilisers; 31% of anxiolytics) (92.2% for indications; 7.8% for dosing) ¹¹¹	Martin-Latry, 2007
FR	Temozolomide	Neuro-oncology	Dosing	Adults 18 years and older	Hospital-inpatient	831 patients (2682 treatment cycles for indications mentioned in SPC)	48.1% off-label indication for all patients (28-38% of the treatment cycles are off-label regarding dosing) ¹¹²	Tileul, 2012
FR	Antiplatelet drugs aspirin and clopidogrel	Cardiovascular	Indication	Elderly > 70 years	Hospital-inpatient	219 patients	16.9% ¹¹³	Cadiou, 2010
IT	Drotrecogin alfa activated	Sepsis/Multiple Organ Failure	Target population	Adults 18-70 years	Hospital-inpatient	668 patients	13.6% & 27.8% ¹¹⁴	Bertolini, 2007
IT	mainly Avastin followed by Herceptin and Erbitux, Eloxatin, Alimta, Tarceva, and others	Oncology	Not specified	Not reported	Hospital-inpatient	843 patients	15% (n=127) (it started at 28,3% in 2008 and ended up at 9,6% in 2010). ¹¹⁵	Cioffi, 2011
UK	Mood stabilizers (lithium and antiepileptics)	Psychiatry	Indication	18-65 years	Hospital-inpatient	249 patients in total; 75 patients receiving mood stabilizers	28.5 of the total of patients. 94.7% of the patients receiving mood stabilizers ¹¹⁶	Haw, 2005
UK	Various medicines (e.g. cefalexin, magnesium sulphate, nifedipine, lisinopril, diazepam and morphine)	Various indications related to pregnancy and delivery	Indication, contra-indication, dosing, administration route	Adults 18-70 years	Hospital-inpatient	17694 prescriptions	74% (25% off-label for indication; 45% for contra-indication) ²⁵	Herring, 2010
IT	Tirofiban (antagonist of the platelet glycoprotein Iib/IIIa receptor involved in platelet aggregation)	Cardiology	Used off-label= without pretreatment	Adults	Hospital-inpatient	1517 patients	55% of patients with acute coronary syndrome ¹¹⁷	Savonitto, 2005
FR	Intravenous immunoglobulins	Auto immune disease	Indication	All ages	Hospital-inpatient	76780 g of IVIg	71% of this amount ¹¹⁸	Frauger, 2011
IT	Chemotherapeutic drugs	Oncology	Indication	Not reported	Hospital-inpatient	133 patients	75,9% of patients (n=101) ¹¹⁹	Orsi, 2007



OFF-LABEL

DE	Psychotropic drugs	Psychiatry	Indication Duration of treatment	18-89 years	Hospital-inpatient	117 patients (123 discharges from hospital and 584 psychotropic drugs prescribed) in years 2001- 2002. 116 patients (120 discharges from hospital and 698 prescriptions for psychotropic drugs) in years 2003- 2004.	In 2001-2002: 20% of prescriptions were clearly off- label, 19% of prescriptions were probably off-label. Thus theoretical maximum of off- label use of 39%. In 2003-2004: 21% of prescriptions were clearly off- label, 26% of prescriptions were probably off-label. Thus theoretical maximum of off- label use of 48% . ¹²⁰	Assion, 2007
ES	Rituximab	Rheumatology, hematology	Indication, dosing	Adults 18 years and older	Hospital-inpatient	221 patients	37.1% ⁵⁰	Conde, 2009
IT	Used off-label for indication: Hyoscine butylbromide, Clonazepam, diazepam, Morphine hydrochloride, morphine sulfate, fentanyl, bromazepam, Betamethasone, Hydrocortisone, Prednisolone, Dexamethasone, Methylprednisolone Used off-label for route: Ranitidine, Hyoscine butylbromide, Metoclopramide, Alizapride, Furosemide, Chlorpromazine, Ketorolac, Ketoprofen, Promazine HCL, Haloperidol, Levosulpiride, Lorazepam, Chlormethyldiazepam, Midazolam, Dexamethasone.	Palliative care	Indication, administration route	28-96 years	Hospices: freestanding palliative care inpatient units	3555 prescriptions	4,5% off-label for indication; 64,8% for sub-cutaneous route ¹²¹ , Sum: 69.3%	Toscani, 2009



Outside hospital (bold figures are presented in figure 3.4)								
NL	Psychiatric medicines	Psychiatry	Indication	unknown	Mental care institution	95 patients	41% (of which: 54% antipsychotics; 38% benzodiazepines) ³⁵	Hoff, 2013
UK	Antipsychotics: olanzapine, risperidone, quetiapine, other.	Psychiatry	Indication	40-87 years old	Tertiary referral centre- inpatient	50 patients	56% ¹²²	Haw, 2008
FR	Various medicines (a.o. topical corticosteroids, methotrexate)	Dermatology	Indication	Unknown	Hospital-outpatient	1252 prescriptions	14% ¹²³	Picard, 2003
IT	Antipsychotics (second generation: clozapine, risperidone, olanzapine, quetiapine)	Psychiatry	Indication	Adults	Hospital-outpatient	209 patients	52% ²⁹	Barbui, 2002
ES	Ticlopidine	Cardiology and Neurology	Indication, dosing, monitoring	Not reported	Hospital-inpatient, Hospital-outpatient	346 patients	Different indication: 56% of patients interviewed. Different dose: 22%; No agreement with the recommended monitoring of blood parameters: 72% ⁴⁷	Del Pino, 2000
SE	Anti-androgens (bicalutamide)	Oncology	Dosing	<65 to >75 years	Hospital-inpatient, Hospital-outpatient	1406 patients	21% ⁴²	Grundmark, 2012
UK	Psychotropic drugs, mainly risperidone but also zuclopentixol, haloperidol, thioridazine, olanzapine, trifluoperazine	Psychiatry	Indication	20-79 years	Hospital-inpatient, Hospital-outpatient	114 patients	66% of patients ¹²⁴	Ghosh, 2010
NL	Paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, anti-epileptics, antimigraine drugs, antidepressants, benzodiazepines, calcium-antagonists, clonidin, and oxygen.	Neurology (facial pain)	Indication	Adults	Hospital-inpatient, Hospital-outpatient	160 patients	34% ¹²⁵	Koopman, 2010
FR	Anti-Alzheimer's disease medications	Psychiatry	Indication	50-100 years old	Memory units, resource and research centers, private specialists (neurologists, geriatricians, psychiatrists).	16236 patients	6,1% ¹²⁶	Tifratene, 2014
FR	Triptanes	Neurology	Indication, contra-indication	Adults and children	Primary care	20.686 users	16.1% ⁴⁵	Perearnau, 2006



OFF-LABEL

IT	Antipsychotic drugs: atypical or SGAs (clozapine, olanzapine, risperidone and quetiapine) and typical (including all other antipsychotic drugs)	Psychiatry	Indication	>15 years	Primary care	465,061 patients	Atypical antipsychotics: 29,8% Typical antipsychotics: not reported. ¹²⁷	Trifiro, 2005
NL	Antipsychotics	Central nervous system	Indication	0-101 years	Primary care	723 patients	10,4% ⁴³	Boontra, 2011
NL	Various medicines	Various areas	Indication	onbekend	Primary care	2191 ill-founded off-label prescriptions	Betahistine for dizziness: 26.7%; celecoxib for back symptoms: 16.3%; methysergide for tension headache: 15.4%; etorocoxib for back symptoms: 12.5% ³⁴	Gijssen, 2009
SE	Medication indicated for asthma or COPD: short-acting β_2 -adrenergics, long-acting β_2 -adrenergics, inhaled corticosteroids, and fixed combinations of long-acting β_2 -adrenergics and inhaled corticosteroids.	Asthma and COPD	Indication	All ages	Primary care	670 patients	150 individuals were prescribed off-label (this is 22% of the total population or 54% of the undiagnosed population) (15% in 0-17 years; 69% in 18-70 years; 17% > 70 years) ⁴⁸	Carmona, 2014
ES	TNF antagonists: mainly infliximab, also etanercept and adalimumab	Rheumatology	Indication	Adults	Not reported	5150 patients	11% of patients with rheumatic diseases receiving TNF antagonists received the medication off-label. ¹²⁸	Kruessel, 2011



Annex G Other prevalence studies

MS	Medicinal product(s)	Therapeutic area(s)	Off-label aspect(s)	Target group	Setting	Number	Frequency off-label	Year of publication
Reporting of off-label use by HCPs (bold figures are presented in tables 3.1 (children)/ 3.2 (adults))								
UK	Primarily antihistamines, analgesics, oral and dry powder inhaled b2-agonists, antibiotics	Pediatrics	Target population, dosing, formulation, and administration route	0-12 years	Other	482 questionnaires analyzed	40% of respondents (186/465) admitted to knowingly dispensing off-label prescriptions during the preceeding month. ¹²⁹	Stewart, 2007
DE	Propofol	Anesthesiology	Target population	0-16 years	Hospital-inpatient	184 pediatric and neonatal intensive care units	79% of all units ¹³⁰	Kruessel, 2012
PL	Various medicines (a.o. antibiotics, antipyretics, anti-infectives)	Various areas (a.o. respiratory system drugs, infectious disease, analgetics/antipyretics)	Indication	0-18 years	Other	103 respondents	33.9% for antipyretics; 29% for symptomatic respiratory tract infection; 25.8% for antibiotics ¹³¹	Kuchar, 2010
FR	Baclofen	Alcohol abuse	Indication, dosing	Data validation	Other	296 prescribers	74.6% of the prescribers ¹³²	Rolland, 2014
DE	Levetiracetam	Neonatology, pediatric neurology	Target population	Term and preterm neonates	Hospital-inpatient	35 hospitals	46% of all hospitals use this drug off-label for this target population ¹³³	Koppelstaetter, 2011
DE	Levetiracetam	Neurology	Indication	Unknown	Hospital-outpatient	145 replies	81% prescribed levetiracetam off-label ¹³⁴	Steinhoff, 2012
NL	Various medicines (a.o. anticonceptives, betablockers, tricyclic antidepressants)	Various areas	Indication	Unknown	Primary care	464 questionnaires from GPs analyzed	100% ²⁷	Jochemsen, 2009
UK	Benzodiazepines: the commonest were diazepam followed by lorazepam	Psychiatry	Indication, dosing	15-83 years old	Hospital-inpatient	77	94.4% : mostly because the duration of treatment exceeded that of the marketing authorisation (86.7%) or because the indication was unlicensed (48.9%). ¹³⁵	Haw, 2007
UK	Psychotropic medicines (e.g. risperidone, olanzapine, clozapine, valproate)	Psychiatry	Indication, target population, dosing	Unknown	Other	116 respondents	65% prescribed off-label ¹³⁶	Hodgson, 2000



OFF-LABEL

DE	Various medicines	Obstetrics and gynaecology	Not stated	Adults (age range not indicated)	Hospital-inpatient	75 questionnaires	65 physicians (91%) off-label: 34% uterotonics, 28% tocolytics, 23% chemotherapeutics ¹³⁷	Ditsch, 2011
NL	Psychoactive drugs: antidepressants, antipsychotics, anxiolytics and psychostimulants.	Psychiatry	Indication Target population	children	The setting of the child psychiatrists was as follows: independent 23%, academic hospital 10%, ambulatory academic hospital 19%, peripheral hospital 21%, ambulatory peripheral hospital 29%, institution 20%, and other 31%.	115 questionnaires evaluated	% of child psychiatrists using each medication off-label: 71,3% for antidepressants; 19,1% for antipsychotics; 25,2% for psychostimulants; 29,6% for anxiolytics. ¹³⁸	Hugtenburg, 2005
UK	not specified	Diverse	age, dose, indication	children	hospital	151 questionnaires analyzed	90% of pediatricians knowingly prescribe off-label ¹³⁹	McLay, 2006



Annex H Country-specific information with regard to regulation of off-label use

Introduction

This appendix shortly describes specific regulation with regard to off-label use (or the lack of it) in the 21 participating Member States. It does not provide the full legislation on prescribing and reimbursement of each Member State. The information is derived from the interviews, the KCE report and from a number of online sources which are sometimes closely or literally cited. Where this is the case, this is mentioned in the text and/or footnotes as "cited from". When no reference is given in a section, this section is based on the interviews.

Austria

Regulatory

In Austria there is no explicit reference to off-label use in the law. Article 8.1 of the Austrian Medicinal Product Act touches upon it. It states which medicines do not need an authorisation: *if the medicine is to avoid life-threatening diseases and if therapeutic success cannot be reached with any registered drug, for example in paediatric use.* Off-label prescribing is not restricted to expensive medicines or life-threatening diseases.

Reimbursement

In case of off-label prescribing approved of by the head physician, costs will be reimbursed if there is no other (authorized) reasonable treatment or in case that treatment was not successful for the patient and it is reasonable to suppose that the off-label treatment is likely to have an effect. In practice, a prescriber is not obliged to report to the health insurer for what diseases the prescription is issued, only in the rarely case a medicine is very expensive. Then, stricter regulations are in place, where the health insurer requires the prescriber to provide an indication.

Prescriber-patient

Prescribers have autonomy in prescribing, but in each case of off-label prescribing doctors need to justify the medicinal and therapeutic need of off-label use and to show their knowledge of the current standard of care (to the best of their knowledge under given the current scientific evidence available) (§ 55 ÄG). Prescribers have the obligation to tell the patient about off-label prescribing. In case the prescriber does not sufficiently inform the patient, then consent can be judged to be missing or invalid. As a consequence the treatment may be regarded as being unauthorised treatment (§§ 6, 88 und 110 StGB Austria).

Belgium

Regulatory

Belgium does not have specific measures with regard to off-label use, but the Belgian pharmaceutical law provides several options in which – in case of exceptional circumstances - the requirement of a prior marketing may be disregarded, namely in case of:



- Unmet medical need;
- Authorisation for placing in the market has no meaning

The Belgium “Kenniscentrum voor Gezondheidszorg” just published a report on (the legal aspects) of off-label use and suggests how off-label use can be regulated. The KCE proposes a step-by-step plan for 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. KCE summarises it as follows: “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 takes into account factors as the availability or non-availability of an alternative and 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” (page 90). For more details, we refer to the KCE report⁵.

Reimbursement

Off-label use may not be reimbursed, unless exceptionally covered by the “Special Solidarity Fund”. If a medicinal product is not yet on the Belgian reimbursable pharmaceutical products lists, the patient can apply for compassionate use or for reimbursement through the Special Solidarity Fund. This Fund has as its objective the reimbursement of medical expenses for rare diseases, rare indications and innovative techniques which are not (yet) refunded by the compulsory health insurance.^{jjjjjjjj}

Prescribers and patients

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Bulgaria

Regulatory

The Medicinal Products in Human Medicine Act (MPHMA)^{kkkkkkkk} provides the regulatory framework for the pharmaceutical sector in Bulgaria. It was drafted in 2007 to align the Bulgarian regulatory framework with European standards. In 2015 it had undergone 20 amendments. The MPHMA covers the role and responsibilities of the Bulgarian Drug Agency (BDA) and it provides centralized, decentralized and national procedures for market authorisation. It also includes provisions relating to pricing of both prescription and over-the-counter (OTC) medicines as well as the establishment and maintenance of the Positive Drug List (PDL).

Bulgaria has no specific regulations in place for off-label use different from what is arranged at the EU-level. Off-label use is not mentioned in the law, neither in the MPHMA nor in other acts such as:

- Health Law (1 January 2005);
- Health Facilities Law (5 July 1999);
- Ordinance on the Terms, Rules and Procedure for Regulation and Registration of Prices for Medicinal Products (30 April 2013);

^{jjjjjjjj} Cited from: <http://www.arthurcox.com/wp-content/uploads/2015/06/Pricing-and-Reimbursement-Questions.pdf>

^{kkkkkkkk} Cited from http://www.mh.government.bg/media/filer_public/2015/06/16/final-report-with-recommendations-for-reforming_bulgarias_pharmaceutical_sector.pdf



- Ordinance № 4 on the terms and conditions for prescribing and dispensing of medicines (4 March 2009).

Reimbursement

Bulgaria has a Positive Drug List (PDL). To be considered for listing, the medicine must first have marketing approval in Bulgaria, as well as evidence of coverage by health insurance programs in at least five of the 10 primary reference countries. As such, off-label use does not meet the requirements for reimbursement.

Prescriber-patient

There are no guidelines for prescribers on how to handle off-label use. Liability of off-label use lays with the prescribing doctor.

Czech Republic

Regulatory

The Czech Republic's regulatory framework for pharmaceuticals is the Act of Pharmaceuticals.ⁱⁱⁱⁱⁱⁱⁱ According to the Czech law, prescribing is the responsibility of the medical doctor. Off-label use is allowed in very specific occasions: "In the case of suspected or confirmed spreading of disease-producing agents, toxins, chemical substances or in the case of suspected or confirmed radiation accident or disaster which might severely affect public health, the Ministry of Health may exceptionally by its decision issued following an application for an expert opinion of the State Institute for Drug Control temporarily authorise the distribution, dispensing and use of a non-authorised human medicinal product or an off-label use of an authorised medicinal product. In such a case the marketing authorisation holders, manufacturers of medicinal products and healthcare professionals shall not be responsible for the consequences implied by such use of the medicinal product. This shall apply regardless of the fact whether marketing authorisation pursuant to Section 25, paragraph 1 has or has not been granted. The responsibility for defects of medicinal products as stipulated by a special legal regulation shall not be prejudiced...." (Section 8, article 3).

Reimbursement^{mmmmmmmmmm}

Duties and tasks related to drug reimbursements are managed by SÚKL. The reimbursement system is being financed by various public health insurance companies. There is co-payment by patients. The conditions for reimbursement are stipulated by SÚKL in individual procedures triggered by an application for registration, and are subject to regular reviews. Evaluation criteria for reimbursement include: therapeutic efficacy and safety, seriousness of the illness for which the drug is indicated, assessment of the cost-effectiveness and of the impact of using the medicinal product, costs per patient and estimated number of patients treated per year and public interest and anticipated impact of the reimbursement on health insurance funds.

With regard to off-label use: "the State Institute may stipulate reimbursement for a licensed medicinal product also for an indication that is not listed in the summary of product's characteristics, if current scientific understanding provides a sufficient basis

ⁱⁱⁱⁱⁱⁱⁱ http://www.sukl.eu/uploads/Legislativa/Zakon_o_licivech_EN_corr_clean2.pdf

^{mmmmmmmmmm} Cited from: <http://www.arthurcox.com/wp-content/uploads/2015/06/Pricing-and-Reimbursement-Questions.pdf>



for its application and using the said product is the only available treatment option, or if using the said product is cost-efficient compared to accessible treatment" (*literally cited from: <http://www.arthurcox.com/wp-content/uploads/2015/06/Pricing-and-Reimbursement-Questions.pdf>*)

Prescriber-patient

There are no clear guidelines on off-label use nor are there clear statements/measures from professional organisations.

Denmark

Regulative

There is a provision in the act of the authorisation of the health care professionals that they have the responsibility to treat their patients to the best of their knowledge. Use of medicines for unapproved indications is allowed which means that doctors do not have to follow the SmPC.

*Reimbursement*ⁿⁿⁿⁿⁿⁿⁿⁿ

The Danish reimbursement system is national and financed by the state. Medicines used in the public in-patient sector are fully paid by public funds. In the out-patient setting patients have a co-payment as the public health service reimburses part of the prescription. Reimbursed is given for medicines which has been granted a positive reimbursement status (general reimbursement or conditional reimbursement) by the DHMA. Denmark has three positive lists:

- Prescription-only medicines with general reimbursement status
- Prescription-only medicines with conditional reimbursement status
- OTC-medicines with conditional reimbursement status.

There are no restrictions on reimbursement for off-label use in case a medicinal product has been granted a general reimbursement status. Conditional reimbursement or single reimbursement may also be granted for off-label use.

Prescriber and patient

The Danish Health Authorisation issues clinical guidelines for the whole of Denmark where it tries to describe what could be a standard of a specific disease and how it should be treated. Off-label use is not explicitly recommended, but guidelines could touch upon it. There is debate as to regions would be able to decide whether they would like to make binding off-label guidelines. Regions would like have the authority to do that.

Estonia

Regulatory

The regulatory framework for pharmaceutical is based on the Medicinal Products Act and the Health Insurance Act.^{oooooooo} These do not include off-label use and there are no specific legal measures or regulations with regard to off-label use. Off-label use of medicines, is the doctor's own responsibility. Off-label use can be helpful in the small market that Estonia.

ⁿⁿⁿⁿⁿⁿⁿⁿ Closely cited from: <http://www.arthurcox.com/wp-content/uploads/2015/06/Pricing-and-Reimbursement-Questions.pdf>
^{oooooooo} <http://ee.euro.who.int/E93049.pdf>



Reimbursement^{pppppppp}

Reimbursement of pharmaceuticals in Estonia is based on the Health Insurance Act and on the Regulation of MoSA No. 123, 8.12.2004 ("Procedure for drawing up and amending the list of pharmaceuticals of the Estonian Health Insurance Fund (EHIF), the contents of the criteria for establishment of the list of pharmaceuticals, and the persons to assess compliance with criteria"). The list of medicinal products that are either completely or partially reimbursed is adopted by the Minister of Social Affairs. It is reviewed every quarter. All concerned persons, including manufacturers and professional organisations can request for changes in this list from the Ministry of Social Affairs.

There is no specific reimbursement regulation for off-label use.

Prescriber – patient

As in any other case of using a non-standard or unapproved therapy, patients must be informed according to the general regulation. So, people should be informed that they get off label. In practice this is seldom done.

Finland*Regulatory*

According to a ministerial regulation, the doctor decides what to prescribe. In the regulation it is NOT said that the doctor has to prescribe according to the indications in the SPCs. The doctor has to consider the efficacy, safety and price of medicine but is allowed to prescribe out of SPC. It is said only that the doctor has to investigate the patient and decide on the treatment. There is freedom for the prescriber to prescribe off-label. This is the doctor's responsibility.

Reimbursement^{qqqqqqqq}

Reimbursements for prescription medicines fall under the Health Insurance Act. Decision on reimbursement are taken by the Pharmaceuticals Pricing Board (PPB) which operates under the Ministry of Social Affairs and Health. PPB first decides on the question whether the medicine is reimbursable for the indications listed in the marketing authorisation document, and then adopts the reimbursable wholesale price. Criteria for to evaluate reimbursement include the therapeutic value of the medicine as well as the costs of the medicine compared with its benefits. PPB independently decides on reimbursement. The reimbursement status is only granted to a medicine indicated for the treatment of a disease or the alleviation of symptoms. As such off-label use is officially not reimbursed.

Prescriber-patient

Prescribers are responsible for the decision to prescribe, which includes the decision to prescribe a medicine off-label. Patients should be properly informed and informed consent.

^{pppppppp} <https://www.ravimiamet.ee/en/reimbursement-medicinal-products>
^{qqqqqqqq} <http://www.pif.fi/en/medical-care/medicine-reimbursement>



France

Regulatory

RTU^{rrrrrrrr}

France introduced the temporary recommendations for use (RTU) policy (n° 2011-2012 act), enacted 29th December 2011.^{ssssssss} RTUs are set up at the initiative of the French Medicines Agency: ANSM. ANSM informs the marketing authorisation holder (MAH) about the need of a RTU and asks to provide all available data on the concerned indication. The RTU can be notified, in accordance with the ECJ courtcases to fulfil special needs. This is in case the benefit/risk ratio of the medicinal product is presumed to be favourable in situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no medicinal products having the same active substance, the same dosage and the same form

The RTU notably specifies the indication and the posology of the medicine. The RTU is published on the website of the National Agency and is transmitted to physicians for whom this RTU is relevant. The RTU includes the obligation for the MAH to set up a follow up of patients based on safety and efficacy information, and real conditions of use. Data gathered through this reporting are sent regularly by the MAH to ANSM that may, where relevant, modify, suspend or withdraw the RTU.

The Ministry of Health, the French national authority of health (HAS), national health insurance, the national cancer institute, centers of expertise for rare disease are invited to report to ANSM off label uses if they believed that an RTU may be elaborated

The law provides also that the MAH contributes to the correct use of their products, that is, they monitor prescriptions' adherence to MA, to the temporary use authorisation (ATU) or to the RTU. When companies are aware of an off label prescription of one of their medicines, they have to take appropriate measures to inform professionals and they have to inform immediately ANSM. MAH have to notify ANSM when they are aware of off-label prescriptions.^{tttttttt}

Other

For products that, in the absence of a RTU, prescribers are free to prescribe a medicine off-label in case an appropriate alternative authorised medicine is absent and the off-label use is expected to improve or stabilise the clinical condition of the patient.

The Code of Public Health provides that enterprises contribute to the proper use of medicines they market. They should take all measures they deem appropriate to inform health care professionals if they ascertain use outside the marketing authorization requirements, the ATU, the RTU or authorization parallel importation. They also have to inform ANSM without delay.

^{rrrrrrrr} Text on regulatory aspects is derived from questionnaire as filled out by representatives of four divisions of ANSM.

^{ssssssss} Detailed information: <http://ansm.sante.fr/Activites/Recommandations-Temporaires-d-Utilisation-RTU/Les-Recommandations-Temporaires-d-Utilisation-Principes-generaux/%28offset%29/0>

^{tttttttt} http://ansm.sante.fr/var/ansm_site/storage/original/application/bd8ccb71932937accccb61fdf15a82ff.pdf



Reimbursement^{uuuuuuuuuu}

General: The mandatory health insurance system (“Assurance Maladie Obligatoire”) covers the entire population. France has two positive lists of reimbursed products: one for outpatient products and one for products used in hospitals. According to Article R. 163-3 of the CSS: “I. Medicinal products are included on the list mentioned in the first paragraph of Article L. 162-17 in the view of the assessment of the medical service provided by such products indication by indication. This assessment takes into account the efficacy and adverse reactions of the product, its role within the therapeutic strategy, in particular with respect to other available therapies, the seriousness of the affection to which it is destined, the preventive, curative and symptomatic character of the medicated treatment and its interest to Public Health. The medicinal products that do not provide a sufficient medical service in the view of other available medicinal products or therapies shall not be included on the list.” Next to that, Article R.161-71-1 CSS requires a medico-economic assessment is required within the framework of the inclusion or renewal of inclusion on the lists of reimbursed for products that meet the following tow conditions:

- Products having or claiming a high level of ASMR.
- Products which represent a significant expenditure impact for Health Insurance due to its effects on the care system, the professional practices, the conditions of caring of patients and if relevant pricing.

Off-label: Medicines that are off-label used are not reimbursable under the health insurance law. Prescribers have the obligation to mention that a medicine is prescribed off-label. However, in reality this requirement is not met. A medicine covered by a RTU (granted by the French Agency (Article L.162-17-2-1 of the CSS) can be reimbursed by the national health insurance. In that case, if the product is already reimbursed for one indication, the same conditions on reimbursement apply for the off-label use.

Validation of off-label use ANSM enshrined as part of legitimate RTU support decision by the community. In the absence of validation by the health authority, any decision to support the insurance of a drug off-label engage the responsibility of the authorities to use this as the administration has neither the legitimacy nor expertise to allow the use of a drug

Prescriber –patient

Physicians must inform the patient of the non-compliance of the prescription with the MA, of the lack of appropriate alternative medicines, of the related risks, and of the medicine’s limitations and likely benefits. The prescription must bear the words, “Off-label prescription”. Physicians must also collect and transmit monitoring data on their patients to the pharmaceutical company in question according to the modalities set forth in the monitoring protocol appended to the RTU. This data collection is crucial to the off-label use of the medicine (cited from ANSM, Temporary Recommendation for Use (RTUs) Principles and information on the methods used by the ANSM for establishment and implementation, October 2012).

^{uuuuuuuuuu} Closely cited from: <http://www.arthurcox.com/wp-content/uploads/2015/06/Pricing-and-Reimbursement-Questions.pdf>



Germany

Regulatory and reimbursement

The medical profession is a liberal profession (§ 1 Abs. 1 BÄO), which implies that physicians have the freedom to prescribe the medicines that are necessary according to them, also if this is off-label. Yet, there are conditions that have to be met; see below, under Prescriber and patient.

With respect to reimbursement, the Federal Ministry of Health is empowered to appoint and commission expert panels “to determine in which cases authorized pharmaceuticals can be used to treat diseases, even though the pharmaceutical has not been authorized for the disease in question [...]” (literally cited from KCE report); at present there are three off-label expert commissions, in the fields of oncology, neurology/psychiatry and internal medicine. The Joint Federal Committee of Physicians, Dentists, Hospitals, and Health Insurance Funds (GBA) then decides which of the assessed pharmaceuticals prescribed for off-label use are subject to reimbursement and thus can be included in part A of appendix V of the Pharmaceutical Directive⁶

In 2005, a ruling of the Bundesverfassungsgericht strengthened the grounds for reimbursement of off-label prescribing. According to this ruling, the costs for off-label use should also be refunded if there are only weak references for efficacy, on condition that the patient suffers from a life threatening condition and alternatives are missing. This ruling is based on the fact that the previous requirements were deemed to be not in compliance with the fundamental rights stipulated in the German Basic Law. As of 2006, the Bundessozialgericht further specified and liberalised the requirements. From then onwards a physician has the possibility “not to decide by himself for off-label drug prescription, but to get a vote of credit from the accordant health insurance company”. If his demand is declined, he has the possibility to write a private prescription. If a physician does not comply with these provisions, he may be called to pay for the off-label prescription. (section almost literally cited from KCE report)⁶.

In many rulings, German courts have laid down that if a medicine is administered for the therapy of a chronic and serious disease, a seriously debilitating disease or a disease that is life-threatening, for which no other satisfactorily therapy is available and for which reliable safety data can be obtained, the medicine will be reimbursed within the system of the SHI (literally cited from: <http://www.arthurcox.com/wp-content/uploads/2015/06/Pricing-and-Reimbursement-Questions.pdf>).

So, medicinal products used off-label are subject to reimbursement by statutory health insurance under the condition of a severe disease where an approved therapeutic option is not available and, in that case, if scientific evidence of the off-label use is given either by scientific literature or by authorisation of the indication in other countries. If all the requirements are fulfilled, the health insurance will have to reimburse.

Prescriber and patient

Prescribers have the right to prescribe off-label under certain conditions. The patient needs to give informed consent. Off-label use can lead to criminal penalties when off-label-use of a medicine was against the approved standards of medical science, i.e. when it is malpractice. The KCE-report stated (page 68): “Any medical intervention is considered to contain the elements of the legal offense known as physical injury, as defined by §§ 223 ff. StGB; 823 I BGB. Like any other physical injury, medical interventions can be sanctioned under criminal law. However, interventions into the patient's legal domain are considered to be lawful if the patient has given his consent



or presumed consent or in case of a justifying emergency (§ 34 StGB). In case of off-label use, the following considerations apply to the preservation of patients' rights and the medicolegal protection of physicians, according to the highest German court in matters of private law and criminal law, the Bundesgerichtshof: "The patient must be informed of the use of a non-approved medication, because, regardless of its actual quality or safety, the medication still lacks the sanction of official approval, which may be essential for an individual patient's decision under the scope of the Medical Preparations Act⁶."

Greece

Regulatory and reimbursement

In Greece, regulatory and reimbursement of off-label use are intertwined. Law 3816/2010 (Official Gazette A 6/26.10.2010) states that reimbursement funds reimburse medicines only for their approved indications, as defined in the marketing authorisation. However, a subsequent Ministerial Decree (Official Gazette 545/B'/01-03-2012) states that for special cases and according to international bibliographic references, a Committee is established in the National Drug Organisation (EOF) where full applications could be submitted by hospitals, the National Organisation for Health Policy Provision (EOPYY) and other Social Security Funds. The administration and reimbursement of the respective prescriptions is possible only after a positive opinion of EOF's special Committee. Approximately 600-700 applications for high cost drugs are submitted monthly to EOF's special Committee for off-label use. In law 4316/2014 it is stated that off-label indications could be reimbursed if included in therapeutic protocols approved by the Central Committee of Health Council (KESY), but for the application a ministerial Decree is needed (no publication yet). These measures mainly are applied to high cost medicinal products dispensed by hospital or EOPYY's pharmacies. Off label use for high cost drugs is monitored through EOF's special Committee for off-label use.

Prescriber and patient

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Hungary

Regulatory

The regulation concerning pharmaceuticals for human use is laid down in Act XCV of 2005 on Medicinal Products for Human Use and on the Amendment of Other Regulations Related to Medicinal Products.^{vvvvvvvv} This law was amended in 2013.

As of 2008, there is a law in place with a separate ministerial decree that describes how permission can be granted for off-label use. There is a system in place where doctors have to ask for permission to prescribe off-label. It focuses on indication but permission can also be asked for off-label use with regard to dosage or route of administration. Permission (an application licence for off-label use) is given by the National Institute of Pharmacy and Nutrition. Once permission has been provided, the fact that this permission have been provided, will be published. For published permissions, other doctors do not need to ask for permission. Yet, prescribers need to inform the National Institute of Pharmacy and Nutrition that they will prescribe the product off-label. An exception is made for chemotherapeutics. In case these

^{vvvvvvvv}<http://www.iracm.com/wp-content/uploads/2013/01/loi-xcv-de-2005-sur-les-produits-m%C3%A9dicaux-%C3%A0-usage-humain-et-amendement-4440.pdf>



products/indications are mentioned in protocols of health care professionals a simplified application for permission may be submitted off-label use is allowed without special permission. At least 5000 times per year, permission is requested. The policy measure is considered as very useful tool, especially in paediatrics, oncology or in rare diseases. Yet, it is a measure with a large administrative burden for both physicians and authorities.

A new legal framework entered into force by the end of 2015 to waive the requirement for authorisation of the off-label use in emergency situations, in life threatening situations.

Reimbursement

The legal basis of the reimbursement system is Decree of the Ministry of Health 32/2004. There is a positive list for reimbursement. The general reimbursement regulation only holds for on-label use. For off-label use reimbursement can take place on a case-by-case basis. The Health Insurance Fund must take the decision based upon circumstances and costs of the individual treatment and within the limits of its budget. In case there are alternatives this should be taken into account alongside the reasons why these alternatives are not suitable for treatment of the patient.

Prescriber-patient

Doctors have to ask permission to prescribe off-label (see above).

Ireland

Regulatory

There is no specific provision in Irish law to prevent or support the off-label use of a medicine. Such use is necessary and appropriate for certain patients and its use is often in line with products guidelines or published literature.

Off-label use is considered to be common practice and reflects the fact that there are not enough approved products to deal with every medical need. It is considered important in the Irish healthcare context, particularly in paediatrics.

There is no specific provision in Irish legislation for the approval of compassionate use programmes for specific groups of patients with an unmet medical need. Ireland has two exemptions from the requirement that medical products have an authorisation that are relevant to patients for the treatment of conditions where there are medical needs that cannot be met by authorised medicines. These are: 1) supply of medicines through participation in an approved clinical trial; 2) in accordance with the specifications of a practitioner for use by his individual patient on his direct personal responsibility, in order to fulfil the special needs of that patient.

The Advertising Regulations in Ireland require that advertisements comply with the SmPC; therefore off-label promotion of a medicine is not permitted. This is consistent with EU law.

Reimbursement

In Ireland, the Health Service Executive (HSE) provides reimbursement support for medicines (and appliances) across 3 main community drugs schemes and arrangements are in place for the supply of hospital initiated High Tech medicines through the Community Pharmacy Contractor network. Under the terms of various



agreements, products may be submitted for pricing and reimbursement approval to the HSE for use and assessment according to their labelled indications as approved in the Summary of Product Characteristics.

Currently prescriptions do not contain details of the treatment indication which would be necessary to restrict medicinal products to licensed indications for the purposes of reimbursement. However, for certain medicines, pre-authorisation for use by Clinicians may be required which can restrict usage to only the licensed indication(s).

Prescriber – patient

The Irish Medical Council guide to Professional Conduct & Ethics states that "as far as possible [the prescriber] should make sure that any treatment, medication or therapy prescribed for a patient is safe, evidence-based and in the patients' best interests..... [the prescriber] should weigh up the potential benefits with the risks of adverse effects and interactions when deciding what to prescribe."

Italy

Regulatory

Off-label use of medicinal products is possible according to national Law n. 94/98 (the so-called Di Bella law), related to off-label use of authorised medicinal products under the personal responsibility of the prescribing physician and 648/96 national Law, when there are some therapeutic areas with an unmet medical need and when companies do not want to perform clinical trials for a given indication. Off-label use requires the support of phase II completed study.

Reimbursement

General conditions of the reimbursement system are established on a national level and implemented at a regional level by governmental bodies. *After receiving marketing authorisation* by the European Medicines Agency (EMA) or the Italian Medicine Agency, a company may apply for reimbursement on the National Pharmaceutical Formulary PFN (Prontuario Farmaceutico Nazionale). Off-label use can be reimbursed as well, namely in case of application of law 648/96 the off-label use is reimbursed. Besides, law 79/2014 has introduced the possibility of reimbursement of off-label indications for which there are already alternatives on the market, provided that it is supported by robust scientific data and a proper assessment of economic appropriateness has been performed. This recent law which substantially amended a previous law decree (No. 36/2014) was adopted in order to allow general off-label ophthalmic uses of Avastin.^{www.wwwww} As such, since June 2014, reimbursement of non-authorized but cheaper equivalents have been effectively approved within the NHS.

Patient-prescriber

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Lithuania

Regulatory

Measures to regulate off-label use are implemented by the orders of the minister of health. The order regulated that it is possible to treat the patients with a product that is not registered in Lithuania (individual treatment). It is an agreement between physician and patient. The regulation describes how to use off-label products, how the doctor should act in these situations and what documents they need to complete. No English information is available

Reimbursement

General: Lithuania has the following medicines lists for reimbursement:

- List of diseases and reimbursable medicines for treatment thereof (list "A", 100% reimbursement);
- List of reimbursable medicines (list "B" 90% reimbursement);
- Reimbursable aid equipment (list "C" 80% reimbursement);
- List of centrally paid medicinal products (list "D" 50% reimbursement).

These lists are approved by the Minister of Health of the Republic of Lithuania.

Off-label: Only products included in one of the those lists are reimbursed. Each list provides not only for the catalogue of medicinal products but also for prescribing conditions which must be strictly adhered to in order for products to be reimbursed. The only exception is made to medicinal products that are included in the list A and that are for treatment of orphan diseases. Such products may be prescribed for unapproved indication, dosage, etc. and will still be reimbursed (section literally cited from: <http://www.arthurcox.com/wp-content/uploads/2015/06/Pricing-and-Reimbursement-Questions.pdf>).

Prescriber-patient

Off-label prescribing is an agreement between physician and patient.

Malta

Regulatory

The Medicines Act sets the regulatory framework. It includes provisions for "matters connected with the manufacture, preparation and assembly, wholesale distribution, storage, destruction, disposal, advertising and authorisation of medicinal products and any activity connected therewith and the regulation of the sale of medicinal products, pharmacies and related pharmaceutical activities and for any other matters ancillary thereto or connected therewith".^{xxxxxxx} Besides, numerous regulations are in use.^{yyyyyyy} However, there is no specific legislation on off-label use. The prescriber is responsible for the off-label use of a medicinal product.

Reimbursement

Medicinal products which are included on the formulary and which are not governed by a protocol can be used off-label at the discretion of the prescriber in Malta. Certain institutions keep records of products which are used off-label. While protocols usually cover authorised use of medicines, a protocol can cover the off-label use of a medicine, particularly if there are no better alternative medicinal products listed on the

^{xxxxxxx} Closely cited from <http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8924&l=1>
^{yyyyyyy} Closely cited from: <http://justiceservices.gov.mt/LOM.aspx?pageid=27&mode=chrono&gotoID=458>



formulary. Protocols for treatment can be based on effectiveness as well as possibly on cost.

Patient-prescriber

The prescriber is responsible for the off-label use of a medicinal product.

Netherlands

Regulatory

The Medicines Act (2007) provides the regulatory framework for pharmaceuticals in the Netherlands.^{zzzzzzzz} Article 68 of this Act provides that off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use. If protocols or standards are still in development, the physician and the pharmacist are required to consult each other. In line with this, the Medicines Evaluation Board (CBG) and the Dutch Healthcare Inspectorate (IGZ) find that correct off-label use entails the requirements of existing scientific evidence and providing correct information about advantages and disadvantages to the patient.

New regulation is under development stating that as of 2017 health care professionals need to register the indication on the prescription of in-hospital prescribed add-on medicines (both registered and off-label indications).

Reimbursement^{aaaaaaaa}

Reimbursement only takes place in case that the effectiveness of a medicine has been proven. In general, medicines are reimbursed regardless of the indication. For some medicines (those on Annex 2 of the Health Insurance Act) the right for reimbursement is indeed linked to indications, meaning that those medicines are only reimbursed for approved indications. Yet, for some medicines on Annex 2 the Minister of Health has set a clause that also for some non-registered indications these medicines can be reimbursed. This is only the case if:

- the insured patient has a disease with a prevalence below < 150,000 inhabitants in the Netherlands;
- efficacy has been scientifically proved
- there is no registered alternative for this indication.

Prescriber-patient

Patients have to give informed consent for off-label use. Patients can ask for a written consent (art. 451 Civil Law).

In case the profession has developed protocols and guidelines with regard to off-label use, it is allowed (see above). In case these protocols and guidelines are still under development, the prescriber and the pharmacist need to consult each other.

Portugal

Regulatory

Off-label use is not illegal neither restricted. The use of medicines for therapeutic indications or conditions different from the approved ones was clarified by the

^{zzzzzzzz} Closely cited from: <http://wetten.overheid.nl/BWBR0021505/2015-01-01>

^{aaaaaaaa} Closely cited from <http://www.arthurcox.com/wp-content/uploads/2015/06/Pricing-and-Reimbursement-Questions.pdf>



Portuguese National Competent Authority (INFARMED, I.P.) in a public information (Circular Informativa No. 184 / 11.12.2010 CD). The use of a medicine outside the approved indications is the responsibility of the prescribing physician, who understands that a particular medicine is suitable for a given therapeutic indication, given the specific patient's case. The Committees of Pharmacy and Therapeutics and / or Ethics of the NHS, are responsible for the decision about the correctness of the therapy prescribed to patients. The Portuguese National Health Directorate has issued some guidance in specific aspects of off-label use:

- The format of the informed consent for off-label use is considered in a Guideline issued by the Portuguese National Health Directorate (DGS – N° 015/2013)
- The use of a specific medicine in a Guideline about Modified Multiple Sclerosis Therapy in Paediatric and Adult Age (DGS – N° 005/2012)
- The Portuguese National Committee of Pharmacy and Therapeutic has included reference to the use of medicines in some non-approved indications (off-label) with the corresponding clinical support in the national formulary, assuring safeguard of patients through case-by-case approvals at a local level.

Reimbursement^{bbbbbbbbbb}

The Portuguese reimbursement system is controlled, regulated and financed at central/national government level. There are no restrictions on reimbursement for off-label use where such use is manifest from the prescription or other circumstances as the Medicinal Products Regulatory Authority does not issue any regulation on off-label use or based on off-label use.

Prescriber and patient

The prescriber is responsible for off-label use.

Patients have to provide informed consent for off-label use.

Slovenia

Regulatory

Slovenia does not have no specific measures with regard to off-label use. Off-label use is not mentioned in the law. It is conceivable that there is off-label use in medical practice because Slovenia is a small market. This is entirely up to the responsibility of the medical profession.

Reimbursement^{ccccccccc}

The reimbursement process is conducted on a national level by the Sick Fund. Reimbursement is granted by the Sick Fund - Health Insurance Institute of Slovenia (ZZZS) under the Rules on classification of medicines on the list (Official Gazette of RS, no. 53/13. Successful reimbursement applications would result in listing of the product on either "positive list" or "intermediate list". The criteria for the drug lists are defined by Decision on the Classification of Medicines to Lists act (2003). With regard to off-label use, there is "a general requirement that reimbursed medicines are prescribed in line with indications as stated in SmPC, however there is impression that products are also prescribed off-label and such prescribing is tolerated by the Sick Fun".

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Prescriber-patient

Off-label use is the responsibility of the medical profession.

Spain

Regulatory

Medications in Spain are regulated under Law 29/2006 of 26 July, of guarantees and rational use of medications and health care products (Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios).

In 2009, specific legislation on off-label use of medicines was adopted^{ddddddddd} and royal decree No. 1015/2009 established that the off-label use has to be limited to those situations in which no approved alternatives exist, with respect to any restriction of the conditions for prescribing and dispensing established in the authorisation (i.e., hospital medicine only) and the therapeutic protocol of the centre or primary care setting. Off-label use of medicinal products is allowed in other healthcare settings such as primary care. Physicians have to adequately justify the need for treatment in the clinical history of the patients and inform them of the potential benefits and risks, obtaining their informed consent according to the national legislation. While compassionate use is allowed only hospital settings, the off-label use of medicinal products is allowed in other healthcare settings such as primary care.

This means that as of 2009 case by case authorisation for off-label use is not required anymore. As a result of the new regulation, the Agency set up and reviews recommendations for use (or non-use), maintains a system for exchanging information with the regional authorities and informs the Market Authorisation Holder (MAH) about the recommendations of use and the suspected adverse reactions notified to the Agency. The MAH should notify any suspected adverse reactions and provide the Agency with any information related with this off-label use that may have any impact on the recommendations.

After the new regulation came into place concerns on budget issues have increased, especially in the hospital setting. Therefore, regional authorities have put internal procedures in place for off-label use, especially for new, expensive medicines. As such, there is new over-regulation, now at the regional level and therapeutics committees of hospitals perform an evaluation of individual cases and the medical director of each hospital must give individual authorisation for each patient. Moreover, the possibility for the Agency to establish recommendations either on the use or non-use of a given medicine has been used only very rarely.

Reimbursement^{eeeeeeeeee}

Reimbursement is regulated I Medicines Act 29/2006. Criteria for reimbursement include severity of disease, certain patient needs, therapeutic and social value, incremental clinical benefit considering cost effectiveness, rationale pharmaceutical expenditure, budget impact, availability of alternatives and innovation degree. Theoretically, off-label use is not reimbursed, in practice, it is. That leaves the decision making on whether to pay (or not) in hospitals and, secondarily, in regional authorities. In practice, there are no problems with somewhat consolidated off-label

^{ddddddddd} <http://www.boe.es/boe/dias/2009/07/20/pdfs/BOE-A-2009-12002.pdf>

^{eeeeeeeeee} Closely cited from:

http://whocc.goeg.at/Downloads/Conference2011/PraesentationenPPRIKonferenz/Day2_morning_Sitzungssaal_0945_Ferre.pdf



uses of medicines but problems are expected with new, expensive, often niche medicines used off-label from the very beginning.

Patient-prescriber

The Medicines Agency may establish therapeutic protocols and/or recommendations whether or not to use a medicine off-label use, for example in case when a risk to patients may be reasonably expected from off-label use, when medicinal products are subjected to restricted medical prescription, or when off-label use may result in a significant healthcare impact. An example is the Agency's recommendations for the non-use of growth hormone in the recovery of brain and peripheral neurological diseases.

Sweden

Regulatory

Sweden joined the EU in 1995 and has since harmonised its legislation with that of the European Community. Therefore, Swedish medicinal legislation is "essentially the same" as that of the rest of the EU. EC Directives are transposed into acts and ordinances by the Swedish Government and into provisions by the Medical Products Agency. These provisions are published in the MPA's own Code of Statutes, LVFS. EC Regulations are directly applicable in the EU-member states. The authority of the Medical Products Agency to issue regulations is primarily laid down in the Medicinal Products Act (SFS 1992:859) and the Medicinal Products Ordinance (SFS 1992:1752)"
There is national regulation in place to handle unmet medical needs such as Compassionate Use Programs and named patient temporary approval, and authorisation of prescriber category for some medicinal products.

Off label use/prescribing is not specifically mentioned or addressed in the law, other than reporting of ADRs as a result of off-label use, implemented in the national pharmacovigilance legislation by EU harmonisation. There is national legal framework in place to regulate all clinical practice in the health care setting. Off-label prescribing, depending on the definition, is allowed but must be based on scientific evidence and clinical experience. The national authority Health and Social Care Inspectorate is to surveille any illegitimate or inappropriate prescribing, including off-label. Larger patient groups to be treated off-label should be encouraged to be studied in the frame work of clinical trials.

By national law, Drug Committees operate at the local health care level to promote and follow up on evidence-based recommended prescribing in a number of therapeutic areas. At the national level, National health care bodies, professional organisations and authorities produce up to date evidence or professional and care standards, for the different levels of decision making. Dependent on the patient group and condition (e.g. children) these standards and protocols may include off-label treatment based on scientific evidence and clinical experience.

There are regulations for the pharmaceutical industry: it is illegal to advertise indications that are not in the label.

Reimbursement

A new Pharmaceutical Reimbursement scheme was introduced in 2002. The Pharmaceutical Benefits Board (LFN) was appointed by the Government to decide

Closeby cited from: <https://lakemedelsverket.se/english/overview/Legislation/>



whether or not a medicine should be reimbursed.^[2] The following three criteria must be fulfilled for a medicine to be reimbursed: the human value principle (respect for equality of all human beings and the integrity of every individual), the need and solidarity principle (people with more severe diseases are prioritised over people with less severe conditions) and the cost-effectiveness principle (reasonable costs from a medical, humanitarian and social-economic perspective). Normally, all prescriptions will be within the reimbursement scheme unless there is conditional reimbursement. Only a few examples exist where the reimbursement is limited to the registered indications. Besides, there are very few ways to identify violations and there are no hard sanctions.

In January 2016, there was a reimbursement denial for an orphan drug for chronic thromboembolic pulmonary hypertension (CTEPH) for which there are no alternative on-label therapies as well as for pulmonary arterial hypertension (PAH), a condition for which alternative on-label treatments are available. In Sweden, a medicine obtains reimbursement if no other treatments are considered significantly more effective. Reimbursement was denied with the argument that the alternative PAH treatments are frequently used off-label to treat CTEPH. Therefore, reimbursement was only granted in that subset of CTEPH patients that did not respond to off-label PAH treatment. This was the first instance of a reimbursement decision in which a product's off-label use was the comparator.^[3]

Prescriber-patient

Informed consent by the patients is needed for off-label use (like it is for on-label use and all therapeutic interventions). There are two sets of insurances, one applicable in on-label situations (held by industry) and one applicable in off-label situations (held by public health care), in case of patient harm.

United Kingdom

Regulatory

Except for list on the so-called Black and Grey-lists, there is no legal restriction on the medicinal products which may be prescribed by General Practitioners in primary care. These lists contain those particular products that General Practitioners are prohibited to prescribe, either for all indications ("the black-list") or for specific indications ("the grey-list").

Off-label use is considered from several angles (such as reference to guidelines, instructions). Guidance issued by the Medicines and Healthcare Products Regulatory Agency use a prescribing hierarchy:

- (1) use a licensed product (marketing authorisation by MHRA),
- (2) use a licensed product off-label if needed (guidance by General Medical Council; the UK regulatory authority for medical professionals)
- (3) use a non-licensed product.

The GMC Guidance (Good practice in prescribing and managing medicines and devices, 2013) indicates that "when prescribing an unlicensed medicine you must: a. be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy; b. take responsibility for prescribing the medicine

^[2] Section based and cited from: <http://www.tlv.se/Upload/English/ENG-swe-pharma-reimbursement-system.pdf>

^[3] Section based and cited from: <http://www.sidley.com/~media/update-pdfs/2016/01/sidley-austin-llp-global-pricing-newsletter--volume-4-2016.pdf>



and for overseeing the patient's care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so; c. make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine." This is 'soft law'. Health professional prescribers' decisions whether or not to use medicines off-label is generally done in accordance with authoritative clinical guidelines and in line with policies developed and operated by relevant healthcare providers. NICE publishes specific guidance documents, i.e. evidence summaries for unlicensed or off-label used medicines.

In March 2015, *the UK* started the early access scheme which is meant for innovative breakthrough areas. The early access to medicines scheme (EAMS) aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. Under the scheme, the Medicines and Healthcare products Regulatory Agency (MHRA) will give a scientific opinion on the benefit/risk balance of the medicine, based on the data available when the EAMS submission was made. The opinion lasts for a year and can be renewed.

Reimbursement

The UK's national healthcare system is the NHS, which is funded through general taxation. With regard to pharmaceutical, there is no formal reimbursement step or "decision" that has to be taken.

Off-label use: In secondary care, NHS Trusts may restrict the indications for which a product may be prescribed. NICE recommendations and patient access schemes (see Q13) may be limited to specific indications and these may, in practice, prevent off-label reimbursement. However, companies are also seeing cases where NHS Trust formularies list cheaper products for off-label indications, rather than a licensed alternative, in order to save on costs. NICE guidance may also restrict the indications for which a product prescribed in primary care is recommended. However in practice, reimbursement in primary care is difficult to control. Pharmacy reimbursement is based on the product dispensed/used, and not the indication for which the doctor has prescribed the product, save for limited exceptions where a product is on the "Grey List" allowing NHS supply only for certain indications. In other circumstances, the product will be reimbursed under the normal rules, whether or not it is to be used for off-label use (*literally cited from <http://www.arthurcox.com/wp-content/uploads/2015/06/Pricing-and-Reimbursement-Questions.pdf>*)

Prescriber-patient

There are good prescription guidelines. In case it is in the best interest of the patient to prescribe a drug off-label this should be allowed as long as a patient gives informed consent. This is clearly written in ethical parts of guidelines. Doctors have to be able to explain that, and why they prescribe off-label.



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