EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

STAMP 6/30

STAMP Commission Expert Group
14 March 2017

Off-label use of medicinal products

Background

Following concerns arising from Member States, stakeholders and the adoption of a European Parliament Resolution calling for specific action regarding the off-label use of medicines, the European Commission decided in 2014 to commission a study to understand the ramification of the issue of off-label use of medicinal products. The purpose of the study was to obtain a clear description of existing and foreseen practices of off-label use across Member States (drivers, prevalence, national frameworks) and a factual analysis of all parties' positions towards the existing measures and possible tools on the off-label use of medicines.

At the STAMP expert group meeting held on 28 June 2016, the contractor presented a first draft of the study report in order to gather comments from Member States, who also submitted written comments after the meeting. Regarding the legal part of the draft report, the European Medicines Agencies Co-operation of Legal and Legislative Issues (EMACOLEX) was consulted in May and September 2016.

The study report has now been finalised and was made publicly available on 28 February 2017[1] (see attached Executive Summary). The aim is to have an open discussion on the basis of the final study report and other sources of information.

Action to be taken:

For discussion

[1] Available at http://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf

Study on off-label use of medicinal products in the European Union[2]

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.

[2] Study completed by: NIVEL, National Institute for Public Health and the Environment (RIVM), European Public Health Alliance (EPHA) in February 2017. Full report available at: http://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf

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.