Universidade de Lisboa
Faculdade de Farmácia

CHALLENGES AND OPPORTUNITIES OF *OFF-LABEL* PRESCRIPTION

Maria Leonor Casa Nova Barão Dias

Dissertation supervised by Professor Mafalda de Castro Ascensão Marques Videira

Master in Regulation and Evaluation of Medicines and Health Products

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ABSTRACT

The main principle underlying global pharmaceutical legislation is the protection of public health and, as such, before a medicine can be marketed in the European Union (EU), its safety, quality and efficacy have to be proven. The use of medicines outside the approved terms of their marketing authorisation (MA) is considered *off-label*- not in accordance with the label.

The reasons for using a medicine outside the specifications laid down in the label are diverse and complex. *Off-label* use is particularly driven to fulfil specific patients' needs and to respond to unmet medical situations.

This clinical modality is a widespread practice, representing an unavoidable reality in modern health systems. However, due to the lack of rigorous risk-benefit assessment, *off-label* prescription raises ethical issues by posing obvious risks to patient's safety and should, for that reason, only be considered exceptionally.

The various stakeholders involved in the medicines field - regulatory authorities, health care professionals (HCPs), pharmaceutical companies, policy makers and patients- are constantly challenged by the need to manage situations that could arise from an *off-label* use. Therefore, they would benefit from the existence of a universal and harmonized framework on this matter.

Currently, there are no harmonized rules at EU level. Several approaches for regulating the *off-label* use of medicines have been proposed in some members states. Nevertheless, the situation remains unsatisfactory and none of these measures seems to be able to adequately address the problem.

Given the importance and controversy of the topic, it is more relevant than ever to promote discussions to effectively manage the *off-label* use of medicines. This work intends to present a narrative literature review of the subject, in an attempt to describe and characterize this practice. It also aims to discuss the challenges and opportunities associated with certain regulation proposals, as well as the most evident implications and contradictions that could arise from the widespread *off-label* use of medicines.

Keywords: *off-label* medicines use, *off-label* prescription, medicines regulation, marketing authorization, clinical decision

RESUMO

O princípio fundamental subjacente à legislação farmacêutica é a proteção da saúde pública e como tal, um medicamento antes de ser colocado no mercado da União Europeia tem de ter comprovada a sua segurança, eficácia e qualidade. O uso de medicamentos fora dos termos aprovados na autorização de introdução no mercado é considerado *off-label* – não conformidade com a rotulagem.

As razões que motivam a utilização de medicamentos fora das especificações definidas na rotulagem são diversas e complexas. O uso o*ff-label* é particularmente motivado para colmatar necessidades específicas dos pacientes e para responder a situações médicas insatisfeitas.

Esta modalidade clínica é uma prática generalizada, representando uma realidade inevitável nos sistemas de saúde modernos. No entanto, devido à ausência de uma avaliação rigorosa do benefício-risco, a prescrição *off-label* levanta questões éticas, colocando riscos óbvios à segurança do paciente e, por essa razão, deve apenas ser considerada excecionalmente.

Os vários intervenientes na área do medicamento- autoridades reguladoras, profissionais de saúde, empresas farmacêuticas, decisores na área da saúde e os pacientes – estão constantemente a ser desafiados pela necessidade de gerir situações que surgem do uso *off-label.* Assim, eles beneficiariam da existência de um enquadramento universal e harmonizado desta matéria.

Atualmente, não existem normas harmonizadas ao nível da União Europeia. Várias abordagens para regular o uso *off-label* de medicamentos têm sido propostas nalguns estados membros. Contudo, a situação permanece insatisfatória e nenhuma destas medidas parece resolver adequadamente o problema.

Tendo em conta a importância e a controvérsia deste tema, é mais relevante do que nunca promover discussões para gerir eficazmente o uso *off-label* dos medicamentos. Este trabalho pretende apresentar uma revisão narrativa da literatura deste tema, numa tentativa de descrever e caracterizar esta prática. Este visa ainda discutir as oportunidades e os

desafios inerentes a certas propostas de regulação, assim como as implicações e contradições mais evidentes que podem surgir do uso *off-label* de medicamentos.

Palavras-chave: uso *off-label* de medicamentos**,** prescrição *off-label*, regulação de medicamentos, autorização de introdução no mercado, decisão clínica

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ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AIFA	Italian Medicines Agency
ANSM	French National Agency for the Safety of Medicinal and Healthcare Products
BfArM	Federal Institute for Drugs and Medical Devices
EC	European Commission
ECRIN	European Clinical Research Infrastructure Network
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Association
EMA	European Medicines Agency
EOPPY	National Organisation for Healthcare Provision
EU	European Union
EUCOPE	the European Confederation of Pharmaceutical Entrepreneurs
EUROPABIO	European Association for Bio-Industries
FDA	Food and Drug Administration
GBA	Joint Federal Committee of Physicians Dentists, Hospitals, and Health Insurance Funds
GOLUP	Good *Off-Label* Use Practice
GVP	Good Pharmacovigilance Practice
HCPs	Healthcare professionals
HMA	Heads of Medicines Agency
IMI	Innovative Medicines Initiative
KCE	Belgium Health Care Knowladge Centre
KESY	Central Health Council
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
NICE	National Institute for Clinical Excellence
PIP	Paediatric Investigation Plan
PSUR	Periodic Safety Update Report
PUMAs	Paediatric-Use Marketing Authorisations
R&D	Research and Development

RTU	Temporary recommendations for use
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
STAMP	Safe and Timely Access to Medicines for Patients
UK	United Kingdom
USA	United States of America
USP	United States Pharmacopeia

1. INTRODUCTION

The main principle underlying global pharmaceutical legislation is the protection of public health and, as such, a careful medicine risk-benefit assessment. Before a medicine can be marketed in the EU, it requires a MA.[1a] The "authorisation" system of medicinal products has the objective of ensuring standards of safety, quality and efficacy. Within this process, a tight and systemic evaluation assures that the "medicine" including pharmaceutical form and dosage should provide a solution for a defined clinical need based on the scientific evidence (pre-clinical and clinical data). Being so, medicines are approved for exact indications, including pathology, patient age and dosing.[2]

Whenever prescribed out of the approved indications or conditions, the medicine will be used as *off-label*.[1,3–7]

Several medicines are routinely used beyond their approved indications. This clinical modality is a widespread practice, representing an unavoidable reality in the modern health systems. It is being adopted at many levels in different forms.

Implications as well as the added value associated to this clinical decision are a recurring discussion and a known medical *hot* topic.

The EU legal framework for medicinal products for human use regulates the MA of medicines, however there is no specific regulation for *off-label* use. So, whereas market approval of medicinal products falls under the responsibility of the competent authorities, the use of medicinal products in medical practice is a decision taken in the relationship between physician and patient. Most of the countries give the prescriber the freedom to decide once the benefit of individual patient justifies this act.[5,8]

For the safe of legal considerations please consider that, the use of medicines outside the scope of the approved conditions is universally accepted as long as proved adequate and rational. Such an obvious need, though justified in many circumstances, it should be seen as an exceptional procedure.

[a] As established in Directive 2001/83/EC on the Community code relating to medicinal products for human use.

The present work arises from the recognition of "contradictions" in the existing medical practice, namely a widening of *off-label* prescription, and the current legislation of medicines for human use. Implications on patient weakness, insubstantial scientific evidence, legal gaps, and physician's lack of awareness will be critically analysed.

Unprecedented levels of this prescription have raised different questions, namely related to the quality of scientific evidence, safety concerns, dissemination of information, liability and financial implications. Moreover, the possible consequences at the level of regulatory structure could fragile the medicine´s authorisation system and discourage Research and Development (R&D) of medicines.

Several initiatives in the EU were triggered, though the legal gap remains unsatisfactory. In line with this concern, recently, a study on the *off-label* use of medicinal products in the EU was published by the European Commission (EC).[4a] This study pointed out some aspects that need an intervention. However, until now, EU took no additional measure.

The *off-label* use of medicines is mainly motivated by the necessity of broadening the use of a molecule whenever an additional benefit to treat a specific patient is proved. Identified drivers that may lead to this clinical practice, apart from patient related factors are obstacles to straightforward MA process, post-marketing authorisation evidence and aspects connected with the work of HCPs.[4,5]

Thought a patient-centred medicine is the paradigm of the modernity, HCPs in special physicians, policy makers and pharmaceutical industry, herein referred as stakeholders, could have an important role avoiding inertia.

The conflict of interests associated to this issue contributes to the lack of regulation in this field, which in turn could induce degree of liability among the different stakeholders.

Questions about quality of care become particularly challenging. The boundary between clinical researches versus clinical practice could become not recognizable, mainly

[a] The study report was published in 28/02/2017. This study covers the public health aspects related to the *off-label* use of medicinal products and the general objective is to provide a description of existing and planned practices regarding this kind of use across Member States.

when substantial theoretical rationale is hampered by low empirical clinical data. The most dramatic situation emerges from the pressure of public health systems in decreasing expenditures and by doing that, creating substantial concerns regarding the cost-effectiveness of the medication.[9]

All the European countries have raised questions about the risk, ethics and legality of this type of practice which clearly denotes the need of establishment of measures to regulate off-label use.[10] The absence of regulation and lack of oversight may lead to negative health outcomes.[1]

Moreover, owing the "modest" legal protection, physicians would benefit from the existence of a universal and harmonized framework based on an agreed Clinical Management plan for each specific situation. Convergence on new policy rules could be the emerging paradigm for how clinicians and hospitals will be conducted this practice in the future.

1.1. Objectives

Almost twenty years ago, the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Oviedo, 1997) raised the issue of providing safe medicines for patients.[11] Nonetheless, the current regulation on *off-label* use does not provide irrefutable proof of medicine quality, use compliance and data from safety and efficacy assessments, when MA medicines are intended for other indications.

This work seeks to expose the current framework of *off-label* use, namely the associated challenges and opportunities.

Apart from the ethical misconduct that can arise, other questions such as economic and financial impact, pharmaceutical industry management, evasion of pharmacovigilance and others will be focused on this work.

Pharmaceutical companies and clinicians are still urging policy-makers to provide an answer for this lack of normative rules. The question that arises is: should modern medicine produce unequivocal guidance for *off-label* use in clinical practice?

It is our understanding that this matter is of tremendous importance when it comes to human dignity and in particular for vulnerable populations.

1.2. Methodology

Taking this in consideration, a complete and extensive search will be carried out in order to perform a narrative literature review, using the following science knowledge data bases and repositories:

ScienceDirect; "b-on" publications; Pubmed; Pharmaceutical abstracts. The list of articles was searched for studies published up to April 2019. Regulatory sources of information (eg. Competent Authorities web-sites) will also be considered.

The queries will be performed using the following Keywords: *off-label* medicines use, *off-label* prescription, medicines regulation, marketing authorization, clinical decision.

2. REGULATORY ENVIRONMENT AND CURRENT FRAMEWORK

2.1. Marketing Authorisation System

To better understand the *off-label* therapeutic added value prescription, it is important to briefly revise the MA procedure. The authorisation of a medicinal product in the market is a prerequisite for *on-label* use, though it also supports the *off-label*.

The requirements for obtaining a MA are explicitly set out in the applicable legal framework of medicinal products. Nowadays, the EU pharmaceutical marketing authorisation framework is primarily regulated through the Directive 2001/83/EC and Regulation (EC) 726/2004.[12] A MA is required for all medicinal products before being placed on the market in the European Economic Area (EEA).[2,13]

The EC, European Medicines Agency (EMA) and the EU Member State competent authorities are working closely together to assure that all medicinal products for humans introduced in the European market meet the EU standards on quality, safety and efficacy. In this way, the applicant has to submit data to be evaluated, which includes quality, preclinical and clinical evidence for the proposed indication, patient population, dosage, frequency and method of administration. Then, an evaluation is performed by the competent authority in order to grant a MA.[1,4,13,14a] If granted, the MA gives the holder the right to market the product within its terms. [2,5,13]

This restriction on the free movement of medicinal products is justified by the will of Governments to protect public health.[5b] In accordance with these legislations, conditions are established under which the product can be used safely and efficaciously.

Without MA, product clinical information or label discussions about *off-* or *on-label* would be pointless.[1]

[a] Articles 8(3) to 11 of this Directive 2001/83/EC, as well as Articles 6(2) and 31(2) of Regulation (EC) No 726/2004, or Article 7 of Regulation (EC) No 1394/2007. The MA procedure is harmonised at European level to ensure consistency across the European markets.

[b] Directive 2010/84/EU

It is important to note that it appears unequivocal the prohibition to market medicinal products without a MA "*No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use (2) and Regulation (EC) No 1394/2007".*[a]

Summarizing, the MA can be obtained by different procedures as described in table 1.

Table 1 European Procedures to obtain a MA [4,12,15b]

Centralised	• Single MA application to EMA's Committee for Medicinal Products for Human Use, approval in all EU Member States at once • Compulsory for specific categories of medicines (diabetes, anticancer, biotechnological processes, orphan medicinal products)
Decentralised	• Simultaneous MA of a medicinal product in more than one EU Member State • For products not yet been authorised in any EU country is not mandatory to follow the centralised procedure • EU Member State is chosen as reference and takes the lead in the assessment procedure
Mutual recognition	• Medicinal product with a national MA in one EU Member State • Authorised in other EU countries by mutual recognition of this first authorisation • The Member State of first authorisation acts as reference member state and provides the assessment report
National	• MA strictly for national authorisation

[a] Article 6 (1) of Directive 2001/83/EC
[b] Directive 2001/83/EC and Regulation (EC) No 726/2004

Whatever the authorisation procedure, a favourable balance between benefits and risks of a medicinal product in the proposed therapeutic indication and the proposed patient population must be demonstrated.[1,5]

The resulting Summary of Product Characteristics (SmPC) is the basis of information for HCPs on how to use the medicinal product for a specific treatment (indications, dosage, range of patients, duration of treatment, contraindications, frequency and route of administration), setting out the position agreed between the applicant and the competent authority.[5,16] The Package Leaflet is derived from this document being more directed to the patients. The SmPC is authorised by competent authorities of the Member States (in accordance with Directive 2001/83/EC) or, in case of a centralised procedure, under EC Regulation No 726/2004. Upon approval, any change in the SmPC should be submitted to the scrutinous approval of the competent authority.[1,2,5]

2.2. *Off -label* Definition

The expression "*off-label*" has started to be used in United States of America (USA) and can be resumed to an use that has not been approved by the country's medicine authority.[9,15–17] *Off-label* use is particularly intended to respond to unmet medical needs. Not surprisingly, it is often seen in specific patient groups excluded from pre-marketing trials (eg. paediatrics, geriatrics, rare diseases) and in case of a life-threatening or terminal medical condition.[18]

Lifecycle management of medicines is highly regulated. In contrast, its use is not. The *off-label* use emerges from the gap between[1]:

- Pharmaceutical industry and health authorities, in which decisions are taken and extrapolate to general patients; and

- HCPs and patients, in which decisions have to cope with individual medical conditions and treatments.

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

Although *off-label* does not have a straightforward definition it is already recognized for *"Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation. Examples include the intentional use of a product in situations other than the ones described in the authorised product information, such as a different indication in terms of medical condition, a different group of patients (e.g. a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorisation in the country where the product is used."* [3,5a]

It is relevant to clarify that, as stated above, this practice encloses several different situations and not only the use for a different indication.[5,13]

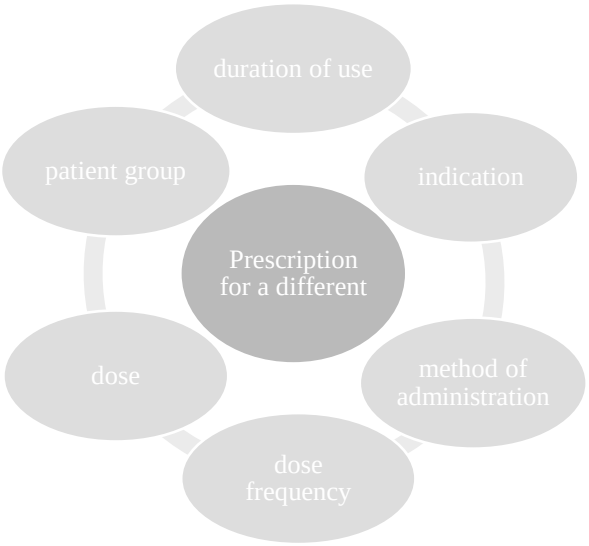

Figure 1 Off -label definition scope

Different modalities can in fact be considered within the theme *off-label*:[19]

Beyond the label	Against the label
prescription considered the uses not included in the MA (eg. use in another disease).	in a situation that is contraindicated in the product information (eg. use in pregnant women, children).

Anyhow, it should be pointed out that the patients medication is not in accordance with the approved conditions of use described in the product information- SmPC.[5,9,10]

[a] This can be read in the Annex I of Guideline on Good Pharmacovigilance Practices (GVP).

The approved conditions define how the product should be used safely and effectively, reflecting the circumstances studied in the clinical trials, the naturally extrapolation to the patients in general as well as data gathered from the *EudraVigilance* system.[13a]

It is important to note that the term *off-label* does not clear imply an improper, illegal, contraindicated, or investigational use.[9,17] In one hand, in terms of commercialization, the European regulatory framework[b] impose that a medicine should be marketed according to the terms of MA, yet recognizing its use outside the approved MA terms (please refer to table 2). On the other hand, in terms of clinical use, the physicians have autonomy and freedom under its Deontological code[c] to prescribe though in the best interests of the patient. This could justify the *off-label*.[4d,9]

Table 2 Although the use outside the scope of the MA terms is not regulated by the EU Law, it is clearly recognized and mentioned in some community legislation

Directive 2001/83/EC	Art 23, "In particular, the marketing authorisation holder shall forthwith […] new information which might influence the evaluation of the benefits and risks […] include both positive and negative results of clinical trials or other studies in all indications and populations, **whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation**." Art 101, "The pharmacovigilance system shall be used to collect information on the risks of medicinal products […] information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation **as well as from use outside the terms of the marketing authorisation**"
Directive 2010/84/EC	"For the sake of clarity, the definition of the term 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and **uses outside the terms of the marketing authorisation**, [...] reasonable possibility of there being a causal relationship between a medicinal product and an adverse event, should be sufficient reason for reporting." Art 23, "**As medicinal products could be used outside the terms of the marketing authorisation**, the marketing authorisation holder's responsibilities should include providing all available information, including the results of clinical trials or other studies, as well as reporting any **use of the medicinal product which is outside the terms of the marketing authorisation.**"

[a] EudraVigilance is the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or being studied in clinical trials in the EEA https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance

[b] Directive 2001/83/EC and Regulation (EC) 726/2004

[c] Regulamento n.º 707/2016 –Regulamento de Deontologia Médica

[d] EU General Court stated, "In the EU, off-label prescribing is not prohibited, or even regulated by law. There is no provision (in EU law) which prevents physicians from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted" Case T-452/14 Laboratoires CTRS vs Commission (2015).

These directives have to be transposed into national legislation. Analysing the Portuguese scenario, the information is compiled into the Decreto-Lei n.º 176/2006, de 30 de Agosto *Estatuto do Medicamento* through Art. 29º (corresponding to art. 23º of Directive) and Art. 166º (corresponding to Art. 101º of Directive).

It is also foreseen in Portuguese Legislation a special type of authorisation for exceptional use "Autorização de Utilização Excecional" (AUEs) [a] that can be applied for a medicine without MA in Portugal. This kind of authorisation is patient specific and has to be justified under certain conditions such as the absence of a therapeutic alternative and in case of a severe or life -threatening situations. It is important to distinguish the situation where the medicine has already a MA in an EU member state for the indication requested vs the case where no valid MA is approved for the concerning indication in other member state. In the last situation, this type of prescription could fit in a "special" case of *off-label* use. However, in the situation of a non-approved indication this request has to be evaluated by Drug Evaluation Directorate of Infarmed.[b]

[a] According to Decreto-Lei n.º 176/2006 and Decreto-Lei n.º 115/2017.
[b] More information regarding this type of authorisation can be found at https://www.infarmed.pt/

Off-label use should be distinguished from the use of unauthorised medicinal products which are products that have not been evaluate by a relevant authority and do not have valid MA in the EU member state where they are being used and thereby are unregistered medicines [5,8] . Nevertheless, these last-mentioned medicines can also be used under specific circumstances, as enumerated in table 3.

Table 3 Legally Foreseen Exceptions- Use of Unlicensed Medicines [4,16,20]

Exceptions of use unlicensed medicines and supporting Legal Provisions
Clinicals trial regulated by Directive 2001/20/EC on the conduct of clinical trials, as set out in Article 3 of Directive 2001/83/EC;
Magistral and officinal products prepared in a pharmacy, as set out in Article 3 of Directive 2001/83/EC;
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."

Although, the approval process of medicines is very robust and strict, there are several parallel situations of medicine´s use, as schematize below.

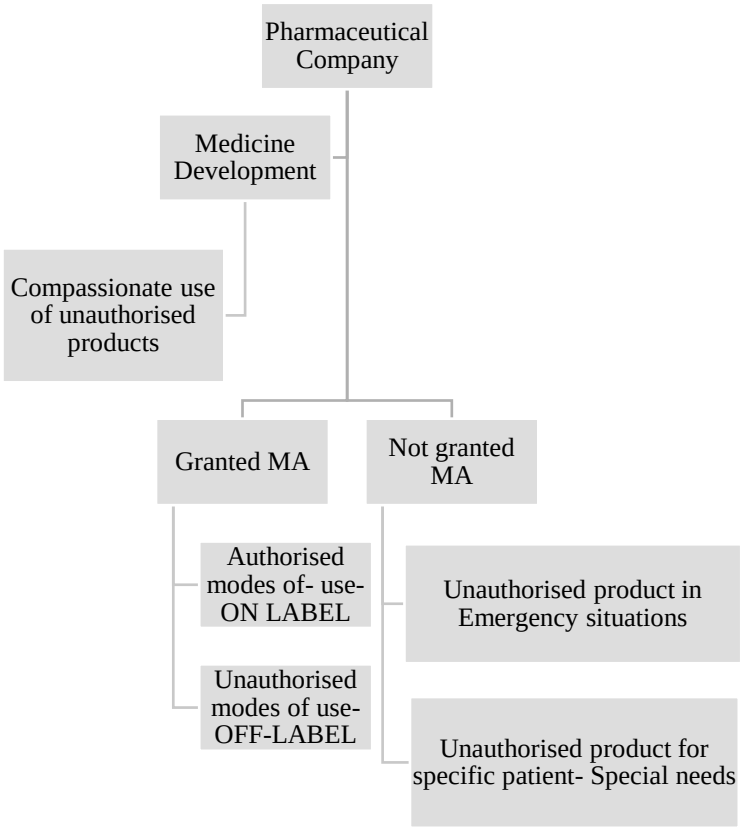

Figure 2 Adapted schematic diagram of Medicines development milestones to show that unlicensed medicines and off-label can be foreseen[21]

As it can be observed, the current MA process substantiate the freedom of medicines use, paving the way to *off-label* use or to unlicensed medicines in the exceptional situations foreseen in table 3. Nevertheless, the latter is out of the scope of our work.

Take this in consideration, it is important to deeply understand the rationales behind the more common *off-label* uses. Such as:

- Medicines that belong to the same pharmacological class, can potentially have the similar effects on the same pathology (eg. use of a statins that were approved for 2nd prevention as 1st line prevention);[7,15,22,23]

- Extension of the use in the stages of bigger severity of the disease than initially study (eg. use of spironolactone in patients with cardiac insufficiency classes I and II, where it was only studied in classes III and IV);[7,15,22,23]
- Use in clinically related pathologies (eg. use of montelukast or salbutamol in chronic obstructive pulmonary disease where it is indicated in asthma);[7,15,22,23]
- Use in diseases with analogue physiopathology (eg. use of metformin antidiabetic in ovary polycystic syndrome);[7,15,22,23]
- Treatment of the similar symptoms of the approved indications (eg. use of gabapentin in situation of pain – non neuropathic origin).[7,15,22,23]

2.2.1. Could we use a medicine in humans evading the Clinical trials?

In order to gather safety and efficacy evidence, the MAH has to conduct different testing phases -Pre-clinical and Clinic Studies.[24–26a]

Accepting the *off-label* concept can lead to a loss of ethical and deontological behaviour, putting the health system under pressure as clinical trials were not undertaken for indications not listed in the approved SmPC.

[a] Pre-clinical studies- Preliminary efficacy, toxicity, pharmacokinetic and safety information. The medicine is tested using in vitro and in vivo, and it is also possible to perform in silico profiling using computer models of the medicine–target interactions. These studies should provide sufficient information to support selection of the initial human dose and safe duration of exposure.

Phase I –First studies conducted in humans, typically involve -Estimation of Initial Safety and Tolerability, Pharmacokinetics, Assessment of Pharmacodynamics and Early Measurement of Medicine Activity, Healthy volunteers or people with the disease/condition (in case of high toxicity of the medicine).

Phase II- The primary purpose is to determine therapeutic efficacy in patients. These trials evaluate the medicine safety for a particular therapeutic indication.

Phase III- The primary objective is to demonstrate, or confirm therapeutic benefit and are designed to confirm the preliminary evidence. These studies are intended to provide an adequate basis for marketing approval and may also further explore the dose-response relationship, or explore the medicine's use in wider populations, in different stages of disease, or in combination with another.

Phase IV- These studies are performed after medicine approval and are related to the approved indication. They are studies that were not considered necessary for approval but are often important for optimising the medicine's use. They may be of any type but should have valid scientific objectives (additional medicine-medicine interaction, dose-response or safety studies and studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies).

It is worth to mention that these medicines´ safety and efficacy have not actually been proven for the *off-label* indication in use, which is serious a dissimilarity when compare with the *on-label* use.

Figure 3 Medicines testing phases

These studies are performed in selected patients according to inclusion/exclusion criteria and do not provide a risk-benefit ratio analysis in special populations, such as paediatrics or eldery.[27a]

The decision to grant or refuse a MA is based on the outcome of the quality, safety and efficacy assessment (by competent authorities) and on the risk-benefit ratio. The risk-benefit ratio focuses on a specific condition in a specific subpopulation, that has been investigated in clinical trials. Consequently, the regulation of medicinal products is based on information about populations of patients using a specific medicinal product, rather than individual patients' characteristics.[5,28]

It should be highlighted that the approval process of a medicine is time-consuming (typically taking 12-15 years), costly (costing a manufacturer around €1 billion), and risky (only 9% of Investigational New Medicines reach the market).[15,29]

[a] Interestingly, according to a French study[27], sixty per cent of reimbursed medicines are prescribed in patients older than 65 years.

2.3. Benefits that drive *0ff-label* Prescription

2.3.1. Fulfil unavailability of a suitable alternative

Thought it is perhaps unfair to evade the regulatory system, unmet clinical needs are in fact the point that motivated the use of medicines outside the scope of MA terms and the more consensual since in clinical practice the best possible treatment for the patient should always be considered, even when no authorised options are available.

The *off-label* use of a medicine increases the options to treat patients, especially in case of:

a) no other approved option available

This is particularly relevant to extend opportunities to treat rare diseases and specific patient groups- mainly pregnant women, paediatrics and elderly -as these groups are frequently not reflected in the product information as the content of SmPC is a reflection of the clinical trials.[1,5,7,8,13,22,34a] Although, the Paediatrics and Orphan Regulations[b] contributed to increase the availability of medicines, some diseases still do not have approved treatment options. These Regulations will be detailed further on.

b) inter-patients' variability - modest outcomes of authorised medicines, emergence of unacceptable side effects

Each patient has specificities related to its clinical situation, making it required to adjust the treatment options to meet the individual necessities. Comorbidities, concomitant medicines and disease progression can influence the medicine´s action and might not be considered in the clinical studies.[c] Only after the medicine started to be used in the clinical practice (non-controlled environment), that some unforeseen aspects raised.

[a] Clinical trials with children and pregnancy woman are more difficult for ethical reasons and frequently exclude elderly due to multi-morbidity. In case of rare diseases, the small number of patients hampers the conduct of clinical trials and the cost of the clinical development process might not outweigh the possible financial return.

[b] Orphan medicines Regulation 141/2000/EC, Paediatric Regulation 1901/2006/EC

[c] Randomised Clinical Trials are conducted in rigorous controlled settings and conclusions based on the study population are then extrapolated to the general population.

Sometimes, the approved medicines for the condition intended to be treated may not produce the expected outcome or severe side effects could arise in a specific patient.

c) medicine shortage

After a MA has been granted, there are several reasons that can precipitate the unavailability of the medicine: disruption in the manufacturing of a product, unavailability of a product in some countries due to economic reasons (especially for lower income countries and countries with a small market) and products may be withdrawn from the market (for safety reasons).[5,13] This can also promote the "health tourism" , not accessible to everyone. While some patients have the possibility to move to another country in order to get the treatment, others not. One might ask where the health access equity is.[30]

In the above-mentioned cases, the importance to ponder an *off-label* alternative is huge to offer a treatment to patients, which will contribute to the decrease of morbidity and mortality.

2.3.2. Extent of Scientific Knowledge and way of gathering Data

Through the *off-label* prescription new treatment options are considered that otherwise, would not be studied or applied. This opens the pathway for innovation and increase disease knowledge and management. However, for this happens, it is crucial that *off-label* uses are closely observed and monitored through the maintenance of accurate and legible records by the physician, including the reasons for their prescribing. These records are the first step to obtain an overview of the extent, safety and effectiveness of such treatments. Additionally, data gathered may serve as an incentive for a more formal study and may play a significant role in adding therapeutic information for other physicians.[8,9,31]

Additional guidance for clinical decision-making may be provided. In practice, HCP recommendations are not always aligned with regulatory approval. Sometimes an indication is recommended as first choice in medical recommendations and is not approved by authorities (eg. methylphenidate used in adults with attention deficit hyperactivity disorder (ADHD) in the Netherlands).[5,19]

Moreover the publication and diffusion of this information through the scientific community is fundamental to the acquisition of new data which could motivate the approval of new uses of medicines.[32a] Considering that clinical research often operates independently from clinical practice, data collection may also play an important role in validating clinical trials results in broader and more diverse populations.[33]

When a clinician reports an *off-label* use, there are different pathways for diffusing that information. The physicians can inform directly peer physicians about the new use for free, or can inform pharmaceutical companies with a view towards commercial diffusion. In the majority of situations, the diffusion is entirely up to the innovating via information freely distributed on the peer-to-peer channel.[34] Nevertheless, physicians have no legal obligation to inform a manufacturer about an *off-label* prescribing.[18]

Spread of information should involve not only physicians but also pharmacists and nurses. Nurses and pharmacists cannot be out of the equation when they are the HCPs that are face to face to patients. Although, in practice, it is not easy to involve community pharmacists as in the medical electronic prescription, and in particular in Portugal, there is no field that identifies an *off-label* situation. This would be of great value to increase the information on this type of prescription and to integrate the pharmacist into the discussion of scientific knowledge.[b]

Associations of patients[c] have also an important role in collecting and disseminating the information. They contribute to the building of evidence by promoting the share of patient's experience. The focus thereof, in particular, lies on those areas that no available options exists.

[a] In the USA, a research has shown that a large fraction (about 60%) of valuable new off-label applications for FDA-approved pharmaceuticals are discovered by practicing clinicians via direct observation of clinical outcomes, or by reports to them from their patients. [34]

[b] In the setting of community pharmacy, the pharmacist in the majority of situations do not have the necessary information to identify an off-label prescription.

[c] For example: https://www.efanet.org/; https://idf.org/our-network/regions-members/europe/welcome.html; http://www.leukotreat.eu/leukodatabase-ethics.php

2.4. Stakeholders involved in the decision making of *off-label* use

Before entering in this chapter, it is worth mentioning that Europe demonstrate interest towards harmonizing *off-label* use of medicines with a patient safety-centred approach.

Prescribing outside of what is approved, tested, presents a risk and can just be justified in exceptional situations.

This type of prescriptions is a real concern shared by all those involved in healthcare system and a risky clinical practice. First for the patient, because risk-benefit ratio is unknown; secondly for the prescriber assuming the legal responsibility, third for the pharmaceutical company accountable but not systematically informed about *off-label* prescriptions and finally for the payer as the cost of the medicine prescribed for a non-approved use will be reimbursed although the prescription is not necessary justified.[27]

Regulators demand rigorous evidence of safety and efficacy, payers want to pay for products with proven quality, and consumers (physicians, patients) want access to appropriate treatments and relevant information.[29]

HCPs and patients are the central players as treatment decisions are in the end the responsibility of the prescribers (until today) who have to search for the best treatment option for their patients. However, other stakeholders are also important and it has been evident the global interest in understanding their responsibility in the *off-label* process (ex. Regulatory Authorities, MAHs, Policy Makers).

2.4.1. Health Care Professionals

Off -label prescription is an exclusive medical practice. The choice of therapy is indeed primarily in the physician's responsibility and should reflect the best possible care, irrespective of the *on-* or *off-label* status. The *off-label* prescription of medicines is covered by the legally recognized principle of the therapeutic freedom.[4,5]

In line with the Deontological code of physicians, this professional group has independence, autonomy and freedom to prescribe according to its conscience and

scientific knowledge acting in the best interests of the patient. Nevertheless, they do have to take into account current scientific progress and medical ethical principles.[8]

The ethical justification for the *off-label* prescribing is to promote the best available therapy for the patient concerned. In some circumstances the omission to consider *off-label* could be considered as a fault.[5] In fact, where no authorized treatments are available, physicians are ethically obliged to search for alternatives.[1,8,9,13,18] In these cases, wouldn't we be violating the beneficence principle if we did not consider the *off-label* use of medicines?

Freedom of prescribing is supported by both, medical judgment and the ability to comprehend the relevant information/knowledge[a] in order to assess the risk-benefit balance that justifies the non-approved use in each specific situation.[15,22,27,28,35]

In daily practice it is often difficult to decide if the intended prescription is sufficiently supported by scientific evidence. Whereas in the case of an approved use the risk-benefit ratio is assessed by health authorities, for an *off-label* use all the burden of responsibility for this decision relies on the prescriber.[18] In situations where both have similar effects, physicians will most likely opt for the approved one, considering the safety issues.

Therapeutic decisions related to *off-label* prescribing are often justified by clinical and scientific facts supported on Evidence-Based Medicine (EBM).[8b] It is expected that these professionals along with pharmacists and nurses are looking forward to knowledge update, allowing them to decide consciously.[c] At this point, it is perhaps important to define level of firm scientific rationale, apart from professional standards and available literature.[1,8,9,18,31]

The absence of recommendations to support clinicians in their decisions raises questions about safety since no risk-benefit analysis can be done without clinical data.[17]

[a] We would like to consider the scientific articles, epidemiologic studies, peer-reviewed journal articles, clinical recommendations of hospitals and institutes.

[b] Evidence- Based Medicine could be described as "integrating individual clinical expertise with the best available external clinical evidence from systematic research".

[c] However it has been reported that only about 30% of off-label prescribing were supported by adequate scientific data.[49]

Nevertheless, physicians are attempt to follow the principles emanated by the GOLUP Declaration concerning Good Off-Label Use Practice. [36a]

Table 4 Main Principles of GOLUP Declaration [36]

• Presence of a medical therapeutic need based on a current examination of the patient by a suitably qualified HCP; • Absence of authorised treatment and licensed alternatives tolerated by the patient or repeated treatment failure; • A documented review and critical appraisal of available scientific evidence favours *off- label* use to respond to the unmet medical need of the individual patient; • Patients (or their legal representative) must be given sufficient information about the medicines that are prescribed to allow them to make an informed decision; • Presence of established reporting routes for outcomes and adverse events linked to *off-label use*.

It can be seen, the need to instigate critical thinking among HCPs - physicians, pharmacists and nurses - whatever the chosen way to do that. Likewise, more public funding should be allocated to support independent continuing medical education to strengthen HCPs' skills on evidence-based medicine (eg. critical assessment of information on medicines).[12]

Physician's´ lack of awareness of the regulatory process in general, the perception that labels are not meaningful guides for clinical practice and the recognition of alternative mechanisms for ensuring safe, rational, and evidence-based prescribing were identified as possible triggers to the *off-label* prescription. This appeared to be, in part, because the primary sources of medicines information utilised by the physicians were formularies, personal and colleagues experience rather than regulatory labels.[37] Additionally, physicians are not always aware that they are prescribing *off-label* once during the (electronic) prescription process no warning is given on this.[4,20]

Nowadays the crisis between the physician paternalism and patient autonomy is globally solved. Patients are now confronted with technical information, that sometimes, they do not even understand, provided to allow them to decide on their disease management.

[a] The Declaration for Good *Off-Label* Use Practice (GOLUP) is supported by a coalition of European organisations that are dedicated to ensuring that high standards of patient care are upheld and that progress in medical research and innovation is achieved.

Although standards vary substantially among the relevant authorities, it is generally believed that prior to any *off-label* treatment, physicians must comprehensively inform patients of the risks and benefits associated, including that it is not approved for the particular indication while explaining clearly the reasons for suggesting the treatment. In addition, they must mention available alternatives. As the decision must be shared with the patient, an inform consent should be obtained.[1,8,15,18,38,a] Nevertheless, case law across Europe indicates that failure to obtain such an informed consent constitute a violation of the duty of medical care.[18]

In this regard, some authors refer arguments to oppose any routine requirement for disclosure: detailed information may frighten patients and the extensive burden placed on physicians to constantly review and communicate medication risk and benefit information may divert attention away from other more important patient care issues.[22]

In July 2012, EU implements the pharmacovigilance legislation, with significant implications for HCPs as responsible for reporting suspected adverse reactions related to *off-label* use. The reports rates are lower than expected due to liability reasons.[5,18]

Another HCP who could play a role with respect to *off-label* use is the pharmacist. Both in hospital and in local pharmacies, pharmacists could be involved in the decision and in the monitoring of outcomes, being trained in pharmaceutical care.[1b] In general, hospital pharmacists are more familiar with this kind of prescribing as they assume an active role in Pharmacy and Therapeutics Committees: assessment of evidence levels to support the prescription choice as well as the need, efficacy, safety and cost of such treatment. They can also be involved in the creation of forms and protocols to support treatment decisions. This group of HCPs has the obligation to inform patients regarding the safe and effective use of a medicine and to validate the medical prescription.[c]

[a] Curiously, a 2013 UK study found (in an online survey with selected clinicians, nurses, and pharmacists in the area of palliative medicine) that only 15% of their institutions regularly inform patients on the consequences of off-label use of medicines, and 22% of the clinicians stated that they never "draw (the patient's) attention to the license" in case of prescribing a medicine which is routinely used off-label. [14]

[b] In the Dutch legislation "the dispensing pharmacist has to be consulted before an off-label prescribed medicine can be dispensed in situations where the treatment has not been taken up in professional standards".

[c] This responsibility specifically includes evaluating the appropriateness of prescribed treatment for the patient.

In the HCPs' perspective, *off-label* use increases the treatment options as in some cases, the best available evidence may not be reflected in the product information. This allows to accept new research results even while they are not yet approved and the discover of new indications and practices based on recent evidence. Taking into consideration the long process of the approval of medicines by authorities, in some urgent situations this could expedite the availability of the treatment to the patient.[4,17]

2.4.2. Regulatory Authorities

Regulatory health authorities regulate the MA process and the content of the label but not the way the products are ultimately used in medical practice.[18] Off-label prescribing resides in a regulatory "no-man's land".[39]

Contrary to medicine prescribing, promotion of medicines is strictly regulated by law and authorities, being limited to the information that is contained in the authorised product information, SmPC. [1,18a] *Off-label* promotion is an illegal practice in all countries worldwide. According to the publicity legislation of medicines, penalties will be applied in the situations where is verify the promotion of an unapproved indication.[6,14b]

For instance EMA, Food and Drug Administration (FDA) as well as the other national regulatory authorities are responsible for ensuring the quality, safety and effectiveness of the medicines that are placed on the market.[8,12,13] The specialized committees of these agencies evaluate medicines based on the proposed indications by MAH that are supported by clinical trials data and further included in SmpC.[9,40] The use of medical products in situations where do not exist clinical data cannot be supported by the assessment of risk-benefit ratio.[1] Furthermore, they have no legal power to enforce MAH to update the product information -include new indications, new administration route, extend population groups in the SmPC-even when adequate evidence is available.[4]

[a] Article 91 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[b] Non-compliance can lead to fines of up to 5% of the marketing holders' EU turnover for medicines approved through the centralised procedure.

It is upon the MAH, the decision to submit an application. In accordance with Article 6 of Directive 2001/83/EC, any variations to the pharmaceutical forms, administration routes, presentations as well as additional strengths and extensions to MA, must also be granted an authorisation or be included in the initial MA.[5,2a] In case of new indications[b] clinical and pre-clinical data are usually required.[5,41] Although, the procedural effort and fee cost of such variation is relatively low and strictly regulated, pharmaceutical companies may lack incentives to develop new indications.[c]

Some national authorities have issued clarifications regarding its role in the *off-label* use. For example, the Portuguese INFARMED, I.P. through *Circular Informativa N. º 184/CD* clarifies that information outside the SmPC should not be evaluate by this institute. The documents highlighted the prescriber responsibility together with the Pharmacotherapeutic committees of each institution whenever they are required to pronounce about the adequacy of prescribed medicines.[40]

However, as public bodies, one would expected, due to its mission to monitor and ensure the safe use of medicines and therefore, they could support physicians in their decision.[36] Different positions on this matter have been assumed in the EU, though it is not possible to interfere with the freedom of prescription, in order to fulfil their duties of monitoring medicines, the EU creates the *EudraVigilence* system. Under the umbrella of the pharmacovigilance directive, the authorities are reinforced, especially in case of non-approved uses.[6] They have to consider in the risk-benefit balance evaluation information

[a] Depending on the type of variation different procedural steps applies. If the changes to a MA are considered to fundamentally alter the terms of the MA, the change has to be treated as an "extension". As stated in the Annex I of the Regulation No 1234/2008, an extension procedure applies in case of :1. changes to the active substance(s); 2. changes to strength, pharmaceutical form and route of administration. Changes to introduce a new therapeutic indication or to modify an existing one as well as variations related to significant modifications of the SmPC (e.g. inclusion of a new target population, changes in posology ,etc.) are classified as major variations of Type II.

[b] A new indication must be understood as a new target disease, different stages or severity of a disease, different age range or other intrinsic (e.g. renal impairment) or extrinsic (e.g. concomitant product) factors, change from the first line treatment to second line treatment (or second line to first line treatment), or from combination therapy to monotherapy, or from one combination therapy (e.g. in the area of cancer) to another combination, change from treatment to prevention or diagnosis of a disease, prevention of relapses of a disease, change from short-term treatment to long-term maintenance therapy in chronic disease.

[c] A survey was conducted for the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP). It concluded that six of 18 participating Member States considered that significant regulatory barriers exist to the addition of new indications to MAs of approved medicines.[73]

resulting from an *off-label* use and eventually impose any regulatory activity to MA (suspension, revocation or variation).[5]

There is a public health imperative to monitor the safety of medicines when used *off-label* as many factors (age of patients, range of comorbidities, use of concomitant medication, medicine-disease interactions, differences in pharmacokinetics and pharmacodynamics) could affect the response of the medicine in a different way compared to the *on-label* use.[8] Medicines with positive risk profiles in the approved indications can demonstrate a negative safety profile when used in non-approved indications or populations not previously studied. [7,23] Based on systematic evaluations in the context of post-marketing surveillance programs, it was concluded that serious and unknown adverse reactions are frequently associated with *off-label* uses for which no scientific evidence exist. [18] In section 2.7 this question will be more detailed.

Within the legislation of pharmacovigilance introduced in 2012, a bigger attention is given to *off-label*. Therefore, the pharmacovigilance Directive 2010/84/EU clearly recognises that the MAH's responsibilities should be widened to any use outside the terms of the MA (please refer to table 5).[5]

Table 5 Obligations of MAHs in relation to the collection and reporting of information related to the off-label use of medicinal products[42]

Reporting of individual cases of *off-label* use associated with suspected adverse reactions	MAHs has the obligation of reporting to competent authorities of any suspected adverse reaction related to the use of a medicinal product to the competent authorities, independently if the use is in *on* or *off -label*. (Article 107(1) and Article 107(3) of Directive 2001/83/EC and Directive 2010/84/EU)
Periodic reporting of the clinical importance of risks related to the *off-label* use of a medicinal product	Periodic Safety Update Report (PSUR) should take into account the clinical importance of a risk in relation to the *off-label* use in the risk-benefit analysis presented. (Chapter VII.B.5.18.2 of GVP Module VII)
MAHs has the obligation to collect of data on the use of the medicinal product	MAHs should be responsible for continuously monitoring the safety of their medicinal products and have to report to the competent authorities any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned, including data on the use of medicine outside the terms of the MA (Article 23(2) of Directive 2001/83/EC)

Risk management planning based on the quantification of *off-label* use in the context of particular risks and concerns	The monitoring of *off-label* use is particularly relevant for known safety concerns in the non-studied population. Potential or identified risks arising from the *off-label* use of the product should be considered for inclusion in the safety specifications. (GVP Module V) When the *off-label* use is considered to raise a safety concern, the risk management plan should be used to clarify the obligations of the MAH regarding: the collection and follow-up of cases of *off-label* use (including cases not associated with suspected adverse reactions); additional structured investigations (medicine utilisation studies, searches in databases). For products without a risk management plan, MAHs and competent authorities should consider whether *off-label* use constitutes a safety concern. If it does, then consideration should be given to requiring a risk management plan.

Competent authorities can also require MAHs to perform post-authorisation studies, yet not for *off-label* indications. There is no obligation to monitor and report on the efficacy in case of *off-label* use (only on safety-adverse medicine reactions), neither for MAHs nor for HCPs. The absence of gathering real world data impair the possible extension of scientific evidence.[4]

Conscious of the situation, European legislators have created incentives in order to encourage R&D activities through the compensation of the pharmaceutical companies' investment and/or facilitating the registration and approval of new medicines in specific areas such as rare diseases and paediatric medicines (areas where off-label prescription assumes a strong expression).

In 2005, the EU Data Exclusivity Directive 2001/83/EC as amended by Directive 2004/27/EC, provides a harmonized data exclusivity period for all the Member States (8+2+1 years). A pharmaceutical company introducing its product to market in the EU can enjoy eight years of data exclusivity, two years of marketing exclusivity plus one year extension.[5]

Table 6 Two types of possible extended marketing protection can be distinguished.

Extension of the ten-year period in the case of new therapeutic indication +1 year market protection	**One-year period of protection for new indications of well-established substances + 1 year data exclusivity**
In case of authorisation of new therapeutic indications representing a significant clinical benefit in comparison with existing therapies.[2,5] MAH should provide scientific data and documentation (in general supported by results of comparative clinical studies) [2,5] New indication must be approved during the first eight years since the initial MA has been granted. The overall period of protection cannot exceed eleven years.[2,5] The additional year of marketing protection applies to the global MA for the reference medicinal product. Generic products, with or without the new therapeutic indication, may not be placed on the market until expiry the eleventh year.[2]	A non-cumulative period of one year of data exclusivity will be granted for a new indication for a well-established substance[a] if significant pre-clinical or clinical studies in relation to the new indication were conducted.[2,5] The significance of the pre-clinical or clinical studies will be assessed by the Agency on a case-by-case basis. [2,5]

According to data published by the EMA, 244 extensions of indications for 127 products were granted between 2004 -2011 and only eight extensions of market exclusivity were approved.[5] Can we assume that additional year for well-established substances is not an effective incentive?

The EU through Paediatric 1901/2006/EC and Orphan 141/2000/EC Regulations, propose to encourage access to medicines for children and rare diseases[b] by providing incentives for the research, development and marketing of these medicinal products that the pharmaceutical industry would be unwilling to develop under normal market conditions.[5]

[a] A well-established substance is an active substance included in the authorised medicinal product which can be shown to have a well-established use in accordance with the requirements of Part II of the Annex to Directive 2001/83/EC as amended by Directive 2003/63/EC.

[b] Affecting not more than five in ten thousand persons in the EU.

Table 7 Summary of incentive measures introduced by EU Paediatric and Orphan Regulations

Orphan medicinal products Regulation 141/2000/EC[4,43]	**Medicinal products for paediatric use Regulation 1901/2006/EC**[4,44]
MAH are eligible to benefit from the following incentives: Assistance with development of the medicine (protocol assistance); Direct access to the centralized procedure; Reduced fees for pre-authorisation and post-authorisation activities; Supporting research by providing funds; Protection from market competition once the medicine is authorized by offering a market exclusivity of 10 years for the orphan indication-during this period, other applications for MA or for extension of an existing MA for the same therapeutic indication must not be accepted by regulatory authorities. MAHs may also request an orphan designation for a product that already has a MA. This would have to be a separate MA for the orphan indication, using a different proprietary name.	Sets up a system of obligations, rewards and incentives, together with horizontal measures to ensure that medicines are regularly researched, developed and authorized to meet the therapeutic needs of children. The Regulation provides sponsors with the right to apply for a six-month extension to the product's supplementary protection certificate (SPC) in return for conducting paediatric studies on the product. The EU as funds for research into medicinal products for the paediatric population shall be provided for in the EU budget in order to support studies relating to medicinal products or active substances not covered by a patent or a SmpC. Paediatric-use MAs (PUMAs) were introduced by this Regulation. Companies can request PUMAs for medicines that are: already authorised; no longer covered by intellectual property rights (patents or supplementary protection certificates); to be exclusively developed for use in children. The development of medicines in children must follow a paediatric investigation plan (PIP) that must discuss all paediatric subsets, as agreed by the Paediatric Committee. PUMA will benefit from 10 years of market protection as a reward for the development in children.

Looking into the impact of these two Regulations 10 years after their implementation:

-According to the 10-year Report of the EC, the Paediatric Regulation has proven to be effective in stimulating paediatric development of medicines as demonstrated by the high number of agreed PIPs[a], paediatric clinical trials, and new medicines for children. Nevertheless, only two PUMAs have been authorised and just 14 PIPs were proposed for the investigation of cancers that are specific to childhood.[45] Can we conclude that the

[a] At the date of report publication (October, 2016) approximately 100 PIPs have been completed and more than 700 are ongoing.

development of medicines for paediatric population is still largely influenced by the adult's medicines investigation?

-More than 850 of orphan medicines designation were provided by European Commission and more than 60 orphan medicines were authorised in EU.[46] This Regulation has benefited the small-medium companies due to the economic and scientific incentives and also due to common initiates (FDA-EMA), which facilitate the administrative burden.

These initiatives show the effort that has been made to fulfil unmet clinical areas, increasing patient's safety through the increase of on-label medicines' availability.

2.4.3. Institutional and Public Policies

Under Article 168 of the Treaty on the functioning of the EU[a], it is established that the authority on organization and conduct of healthcare remains with the Member States. Can *off-label* use be included here?

According to WHO, Health ministries (or social security agencies in some countries) have the responsibility of regulate the behaviour of the different health players and establish appropriate rules and control measures. Institutional and Public Policies should guarantee the public interest where is included the implementation of quality standards of pharmaceutical products, promoting the welfare of the patient.[47] Medicines access, their efficacy and safety should be assured by the governments. They should also guarantee the sustainability of the national health service, through the rationality and efficient managing of medicines and thought the improvement of prescription-dispensing and promoting the development of the pharmaceutical sector.[48]

[a] Consolidated version of the Treaty on the Functioning of the European Union – Part 3: Union Policies and Internal Actions – Title XIV: Public Health

Whether or not the costs of *off-label* use are covered depends on the health system established in each Member State.[18a] In some member states, there are specific insurance coverage policies where in others the reimbursement is limited to authorised uses.[4b] Therefore, the analysis of cost-benefit should also be considered, especially regarding the fact that the prescribed *off-label* use may not be subsidised by public or private insurers which may lead to a high financial burden for the patient.[15,18,37] In relation to private insurance, it will not be discussed in the scope of this work.

The "payer entity" should have a role in the decision of use a medicine outside the approved conditions as the economic consequences of *off-label* use could be significative and have to be considered. When the reimbursement of medicines is decided, normally just take into consideration the approved indications that correspond to a lower prevalence. So, the reimbursement of unapproved uses under the "approved uses" leads to an increased expenditure, especially in situations of high-priced medicines.[c] In the majority of cases, there is no mechanism in force to control or regulate the *off -label* use. Additionally, handling of the adverse effects could have an economic impact.[1,6,67]

It is important to understand that the system was "built" to manage the normal situations- on the scale of the entire population and not for the exceptions- based on individual considerations. In the case of an *off-label* there is no robust scientific data (or at least, the results of testing have not been approved under an authorisation procedure), which hampers the decision making processes -to determine whether there is sufficient value for *off-label* medicine use to warrant reimbursement.[1,20]

Perhaps the lack of legislation in this field could explained that against what should be expected, some member states are fostering the *off-label* use based on economic reasons to reduce healthcare spending and promote sustainability of the healthcare system.

[a] Directive 2001/83/EC stipulates that "the provisions of this Directive shall not affect the powers of the Member States' authorities either as regards 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".

[b] The last is the case of Portugal, where the reimbursement of medicines is restricted to the approved therapeutic indications and the final decision is from Ministry of Health.[6]

[c] When the hospital uses the product for other indications, it may be assumed by the payers that this can be financed from the "normal" budget which often raises problems for the hospitals, considering the high level of *off-label* prescriptions and so the budget is often not sufficient to pay for this. This leads to inequality between patients, where availability of medicinal products depends on which hospital the patient is treated in.

A very rally illustrative budget pressure situation is the case of interchangeability between Avastin and Lucentis in age-related macular degeneration. Due to price difference, many hospitals substitute Lucentis by Avastin non-approved formulation.[a] This trend towards encouraging *off-label* use by policy makers for financial reasons has been caused friction between national authorities and the pharmaceutical industry and, more important, is considered to be incompatible with the EU regulatory framework. Please refer to the clarification of the European Court of Justice which has ruled that patient safety must always prevail against any economic rationale. Unauthorised practices could create unnecessary and avoidable risks for patients, and lower the scientific standards set out by EU legislation.[1,13,18,36]

European Court of Justice clarified the meaning of article 5[b] (1) of Directive 2001/83/EC, and emphasised that the exemption to the MA requirement cannot be applied for only financial reasons.[4] This clarification was under the case *C-185/10 European Commission vs Republic of Poland* (*"individual situations justified by medical considerations", following "an actual examination of his patients and on the basis of purely therapeutic considerations.").*The Polish Law on Medicinal Products contained a provision that allowed medicinal products to be imported into Poland without a MA on the condition of the price of the imported medicinal products has to be competitive compared to the price of the similar medicine in Poland.[4]

Italian and France have also established practices to promote *off-label* use considering the cost-saving. In January 2015, a complaint against the Italian law of May 2014 which provides for reimbursement of medicinal products used *off-label* even though a licensed alternative is available has been filed by European Federation of Pharmaceutical Industries and Associations (EFPIA), European Confederation of Pharmaceutical Entrepreneur (EUCOPE) and EuropaBio. A further complaint was issued in September

[a] There is a "non-inferiority" clinical trial which concluded that both medicines have equivalent effects in visual acuity (considering 1 year) and that the differences in the frequency of serious adverse events should be better defined.[7] Curiously, the bevacizumab is included in the latest WHO model list of Essential Medicines (21st List 2019) under the ophthalmological preparations, whereas ranibizumab approved for this indication has not been included in this list. [35]

[b] "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."

2015 in relation to an amendment to the French system, which allows the French medicines regulator to issue a temporary recommendation for unauthorised indication, for economic purposes, independently the existence of an authorised alternative treatment.[13]

The absence of clear regulation can lead to acceptance of *off-label* treatment as a comparator in the assessment of the therapeutic benefit in the context of reimbursement decisions for new products. In the Netherlands, if *off-label* treatment is included in the professional guidelines, the MAH of the new product for which reimbursement is sought, may be required to present direct or indirect evidence of added therapeutic benefit over *the off-label* treatment. Passivity on this matter creates a controversial whereas health authorities make decisions on reimbursement for a potentially large patient population based on *off-label* use which is only allowed on the basis of individual decisions.[1]

2.4.4. Patients and Patient Associations

In the exercise of their autonomy, the patient can consent to use a medicine outside the scope of SmPC.

Nevertheless, at the end of the day, this group interest´s is to get the best possible treatment for its clinical situation that should be the principle, the limit and the justification for the *off-label* prescription.

Therapeutic options might get restricted if we do not consider non-approved uses in some patient population. Often, when the best available therapeutic option fails, patient demands new approach or new treatment which ultimately leads to *off-label* uses.[49] In this context, and as already mentioned , this kind of prescription can provide better access of patients to innovative treatments and the fact that unmet medical needs of patients can be fulfilled.[4]

It is a decision that should be shared between the prescriber and the patient. In this regard, the informed consent assumes a crucial role, once detailed medicine information, namely the risks and benefits that can arise, and also alternatives to this treatment, should be included. Although each member state regulates this matter differently, in the majority

of EU member countries, it is establish the patient's right in obtaining information when the prescriber presents the option of *off-label* use.[8, 35]

The Oviedo Convention determines that free informed consent applies to any intervention of public health and should be done by the person concerned, unless exceptions provided in art.º 6 (minor, mental disability). It is also defined the content of the information to be presented to the patient (aim, type and consequences of the intervention).[35] The written consent is only a part of the process, as the transmission of appropriate and complete information in order to allow a truly informed decision assumes major importance.[35,50] Considering the level of the treatment risk, the informed consent process should be adapted.[17]

In some member states the informed consent is included in national law. For instance, in Portugal the written informed consent is expressly requested, in a case of use outside the approved conditions in the hospital setting. (soft law – da Direção Geral de Saúde) and the obligation to provide information, besides be consigned in Physicians Deontological Code of Conduct, is properly consecrated in Law (Lei de Bases da Saúde and Penal Code).[15,35,50,51]

Another downside of this prescribing practice is the more limited amount of information that is available on which the patient has to decide whether or not to accept the treatment.[4] Although patients have the right to decide (under their autonomy), the lack of information to support risk-benefit evaluation contributes to a "blind decision".

Regarding medicines monitoring in terms of safety, a step forward was taken by the EU in an attempt to empower these group of consumers by creating a platform for them to report adverse reactions (*EudraVigilenc*e). This new scenario will surely put downward pressure on the physicians, leading to "recommendation prosecution highway" (as happened with the patents).[14,18a] An EU concerted effort to allow the empowerment of this group has been observed .

[a] The EudraVigilance platform could gather data on adverse effects reported by patients as well as by HCPs. The cross-reference link can expose physicians to an increased liability.

Additionally, patients are getting more involved in their clinical situation and seek the most effective treatment, sometimes based on information they exchange with other patients or by participating in patient associtions.[4]

Scientific and therapeutic activism mainly in diseases with uncertainly or insufficient evidence merge to protect the patients and promoting knowledge dissemination. The activism related to patients' associations can assume special importance in the *off-label*, not only in the field of knowledge but also to support patients autonomy when it comes to give their consent for a non-approved treatment.

Across EU some projects have been emerging such as PatientPartner (www.patientpartner-europe.eu) and VALUE+ (www.eu-patient.eu/Initatives-Policy/Projects/ValuePlus) in order to fulfil patients´ needs. The first, focus on partnership in the context of clinical trials and provides a communication platform and guidelines to enable mutually beneficial interactions between patients and clinical trial professionals whereas the VALUE+ project promotes exchange information, experiences and good practice regarding the patients and patient organisations in EU.

We cannot forget that for certain groups of patients off-*label* can remain the only alternative –paediatrics, rare diseases, pregnant women, geriatrics, burn victims.

2.4.5. Pharmaceutical Companies/Industry

From a regulatory perspective, the long development time and high costs needed to investigate a new indication; preparing a dossier for a MA extension and introducing 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.[1,4]

In situations where the pharmaceutical companies decide to move forward with application of a new indication, delays in granting a regulatory approval even after it has gone through clinical trials and proved to be effective and safe can discourage the companies.[49] This is particularly relevant in case of orphan diseases. Fair nought,

physicians that opt for this type of prescription support their decision in information dissipated far ahead of MA procedures: the medical world may have accepted the beneficial effect of a medicinal product use long before the approval of health authorities.[1,18]

Additionally, there are indications and patient groups that are out of scope of the MAH pipeline, being therefore not expected that the company would have to change all its strategy to mitigate theses needs. Moreover, considering the reality of medicine development , it is practically impossible to conduct research for every possible use of medicine and therefore, prioritisation of clinical research is necessary, owing the priority to those that are more suitable to enter the market.[1a] MAHs make their development decisions – which are also considerable investments – on the basis of commercial arguments. The contents of the dossier are the responsibility of the applicant and the claims made based on the evidence presented. During the development process, the medicine may have a broad scope of potential indications, however the applicant selects a few to follow further research. As the investment and duration required to complete the trials both increase in proportion to the number of indications, MAH are reluctant to include further indications which might escalate the cost and time.[1,37,49,52]

Patent protection has also an important role in pharmaceutical companies' strategy decisions. We have two possible scenarios – 1) patent expired product 2) patented products. In the first situation there is a limited interest from the industry to extend indications. Among those patented, though the legislation allows one-year extra market protection, this additional year provides only limited benefit.

From a business point of view, to seek supplemental approval for new uses late in a medicine's patent life is not very enticing for pharmaceutical companies as the developmental cost of new uses might exceed the benefit of regulatory approval.[49]

An additional concern is that *off-label* use of medicines may undermine the incentives for manufacturers to perform clinicals studies for extending the MA.[18] Moreover, the study results could decrease sales by showing that the medicine is ineffective or has significant safety problems. Could this raise the question whether the industry will

[a] Any delay in getting regulatory approval will shorten the period of marketing for a medicine during patent´s life.

suffer from results that could decrease sales showing that the medicine is ineffective or has significant safety problems? One may think, that owing the MAH's responsibility to continuously monitor the quality, safety and efficacy of its medicinal products together with post-authorisation studies aiming at collecting data to enable the assessment of medicinal products safety or efficacy in everyday medical practice, what was questioned above presumably does not happen.[4,18]

Moreover, as already mentioned in this work, MAH is required to provide to the health authorities any new information which might influence the balance of risk- benefit, including the *off-label* uses.[4,18,a] Throughout the life-cycle of a medicinal product, the MAH has the obligation to update the product dossier according to the technical/scientific progress and new regulatory requirements, making the amendments that may be required through the stablished notification to the competent authorities of the Member States where the medicinal product is authorised.[5,42]

Remarkably, pharmaceutical companies' liability in these cases is not linear. On one hand, they can just be held responsible for issues related to the approved uses, so in case of unexpected events associated with *off-label* prescription, it is unlikely to implicate any legal or ethical responsibility. However, if known the MAH should take possible measures to manage/mitigate the risk (eg. include adequate warnings for risks /side effects in the product information of off-label use).Taking this in consideration, the liability depends on the situation´s outline.[5,7,15,18]

Another point that could raise liability among the pharmaceutical companies is the thin line between scientific and commercial activity. The proactive provision of information by a pharmaceutical company about an unauthorised use of a medicine can be seen as unlawful promotion. However, it is important to clarify if the response to HCPs requests for information by the MAHs could be considered promotion. The context in which such information is provided will determine whether the activity is acceptable or not.[13,52b,69a.]

[a] Directive EC 2010/84/UE

[b] Inquiries must be handled by the company's medical affairs office, not its sales staff, who must provide responses to the question that are narrowly tailored, balanced, and carefully documented.

As already referred, promotion of unauthorized medicines or unauthorized uses is unacceptable once advertising of medicinal features must be primarily informative and based on approved data. Infringements are subject to enforcement procedures and specific measures in the different Member States.[1b,5,12,22] The USA, as usually, has adopted a more permissive attitude once legal decisions determined that dissemination of truthful information about unapproved uses constitutes freedom of speech.[29c]

To close this section, it is worth mention the Innovative Medicines Initiative (IMI)[d] - biggest public-private partnership in the life sciences between the EU (represented by the EC) and the European pharmaceutical industry (represented by EFPIA) -which works to facilitate collaboration between the key players involved in health research, including universities, research centres, the pharmaceutical and other industries, patient organisations, and medicines regulators. The aim of this project is to improve health and the prompt access of patients to innovative medicines, particularly in areas where there is an unmet medical or social need. The shared responsibility promoted by these kinds of partnerships maybe the pathway to manage the complex area of *off-label*. A joint debate is necessary to find solutions that suit all the stakeholders involved.

[a] In the USA, the legal framework does not prohibit the exchange or dissemination of truthful information about a product's unapproved uses in specific circumstances. In 2009, the FDA released guidance on "good reprint practices" for distribution of scientific publications on *off-label* uses.

[b] In the USA, cases of *off-label* promotion regularly reach the headlines of the newspapers. An example is the lawsuit against Warner- Lambert with respect to *off-label* promotion of gabapentin, which resulted in US$430 million fine.

[c] In 2015, the U.S. District Court for the Southern District of New York decided that FDA could not prevent the MAH to use his freedom of speech and, thus, to inform truthfully and non-misleadingly about *off-label* use.

[d] https://www.imi.europa.eu/

2.5. *Off-label* Medicine Prescribing Prevalence

The magnitude *of off-label* use varied widely among specific clinical areas and medicine classes. Prevalence of this practice can be seen either in paediatric and adult population and is higher in specific therapeutic areas (figure 4), as it will be discriminated further on.

Figure 4 Areas with a high level of off-label prescription

Generally, report rates are around 40% in adults and in paediatrics up to 90%.[10,12,15,17,27,34–37] According to *Study on off-label use of medicinal products in the EU*, the literature reports levels of 20% or higher for the *off-label* use and more than 55% when looking at the percentage of physicians prescribing it. It was also found that this practice is more common by specialists than by general practitioners.[4,8]

A systematic review of the international state of the art in this matter points out difference in the rate of *off-label* prescription- 50% in the USA vs 23% in Europe.[7]

It is visible a considerable variation in the estimation of prevalence among the different studies. Disparity in *off-label* prevalence depends on the methodology used and

the population studied (most of these studies are medical record reviews, and, as such, each provides a relatively localised picture of the incidence and patterns).[1,4,53a]

The absence of control and register of this kind of prescription (especially in outpatient setting) makes difficult to determine the accurate prevalence of *off-label* and because of that, there is a high probability of being underestimating.

2.5.1 *Off-label* Prescribing in Paediatrics

Off-label use in children is still widespread and is primarily driven by the lack of medicines authorized for this group. Although, this is obviously a general issue, the EU *Study on off-label use* described infectious diseases, cardiology, dermatology, pain treatment, alimentary tract and metabolism, respiratory system and the central nervous system as the most common areas of *off-label* in children.[4b] Among the literature, it is possible to find several studies highlighting the high prevalence of this practice in this population group.

Table 8 Several authors pointed out the prevalence in the paediatric setting[53]

France	USA	Finland	Germany	Portugal
2000 - 2522 prescriptions (989 patients under 15 years) 29% of all prescriptions were *off-label,* and that over 50% of children received an *off-label* prescription *Chalumeau et al.* (2000) [54] 2014 – at least one *off-label* prescription (550 of 989 patient files examined) in patients under 15 years old-56%. [55]	2007-78,7% of 355.409 children had received at least one *off-label* medicine (hospitalized patients under 18 years)[56] 2009 - 62% of 7901 outpatients (0-17 years) received *off-label* prescribing.[57]	2009 - 36% of all hospital prescriptions were *off-label* - 2/3 of *intpatients* received at least one medicine *off-label* and that is proportional to age. In children older than 11 years prescription drops from 85% to 13%.	2002- 1,74 millions of prescriptions for children under 16 years old found out that *off-label* use rose to 13%.[14] *Bücheler et al.* (2002) [58]	2014- systematic review to assess the extent of the use of *off-label* and/or unlicensed medicines among hospitalised children 42% to 100% of paediatric patients receive *off-label* or unlicensed treatments. *Magalhães et al*(2014) [59]

[a] There are several reasons for this a) various definitions of *off-label* use were applied in the studies; b) prevalence figures are either expressed as percentage of the total number of prescriptions or the total number of patients or the total number of medicines; c) the data sources differed per study; d) the period of the data differed (this may influence the accuracy and precision of the results); e) amongst children, the prevalence may differ per age group; f) studies confined to a specific group of medicinal products vs studies that consider all therapeutic groups.

[b] Naturally, these areas correspond to the ones with less availability of paediatric medicines.

2.5.2 *Off-label* Prescribing in Pregnancy

Also, in this population group *off-label* use is driven by the fact that medicines generally are not tested in pregnant women. The prevalence is largely unknown as there is a lack of empirical data.[4,53] Here, *Eudravigilence* can have a huge contribute to a broader prevalence´s knowledge.

EU Study on off-label use, mentions only a study in which this use occurred in 74% of all prescriptions in pregnant women (45% for contra-indication and 25% for indication).[4]

Another study of inpatient prescriptions for antenatal patients at United Kingdom (UK) hospital (over a 3 month period) found that 84% of medicines approved for use during pregnancy on the hospital formulary are *off-label* or unlicensed, and that these medicines account for 75% of all medicines prescribed.[53]

2.5.3. *Off-label* Prescribing in Rare diseases

In the field of rare diseases, use of medicines for non-approved indications is widespread and driven by the lack of authorized medicines for these specific diseases. According to the information gathered in the *EU Study on off-label use* : 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 another survey, it was 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. [4]

2.5.4. *Off-label* Prescribing in Psychiatry

Patients with psychiatric disorders are often excluded from clinical trials, and these illnesses are inherently difficult to study. Moreover, there is often crossover in symptoms from disease state to disease state, which has lead physicians to use psychiatric medications approved for one psychiatric condition for additional unapproved indications.[8,22,23,29]

According to the *EU Study on off-label use,* the reported prevalence in literature is 25-69% of the psychiatric prescriptions to children and 79-86% of all children treated for psychiatric illness. The percentages in adults are 30-48% considering the prescriptions and 29-66% for the patients. In addition, the study reveals that 65-94% of psychiatrists prescribe *off-label*.[4]

A study (2000) in the outpatient setting in Austria showed that 66,5% of 173 patients received antipsychotics for an *off-label* indication – most commonly for anxiety and sedation.[53] Two USA studies demonstrated, that between 57,6% (372.038 individuals given an antipsychotic medication of which 214.113 received these agents for *off-label* disorders) and 63,62% (21.252 antipsychotic recipients received at least 1 of these medications *off-label* in 2001) of patients with prescriptions of antipsychotics received them for *off-label* indications. In these studies, there was a clear association between *off-label* use and age, with the most occurring in those aged 65 or older.[53]

Another USA study confirmed higher rates of *off-label* antipsychotic use in the elderly, showing that over 85% of nursing home patients (corresponding to 308.990 patients) received these medicines for non-approved uses.[60]

The scenario is similar regarding anticonvulsants:

- A study of USA state of Georgia across both inpatient and outpatient settings in two separate years showed that 71,3 % of patients (34. 676) prescribed anticonvulsants received them for *off-label* indication between 1999 and 2000.[61]
- A study by *Radley* and colleagues conducted in 2006 in the USA outpatient setting demonstrated that anticonvulsants are the class of medicines most commonly used *off-label*, occurring in up to 46% of all prescriptions for this class of medicines.[62]

2.5.5. *Off-label* Prescribing in Oncology

In oncology, frequently the standard of care for a particular type or stage of cancer involves the *off-label* use of one or more medicines.[15,28,31] A “trial and error” approach is

often present, as treatment has to be individualised, because of differences between patients with respect to the resistance to individual active substances of cancer cells. An example of this is the use of combinations of cytostatic agents for cancer patients in specific stages of the disease.[1]

The extent of *off-label* use in children is reported in literature to be 15% (including haematology) up to 43% and 10-76% in adults, depending on the type of cancer.[4,7] Associated costs are generally high considering the type of medicines used in this field (biologic therapies).[7]

A USA study concluded that 30% of all uses in oncology were *off-label*, however for about a third of these medicines the non-approved use was extensive, constituting more than 50% of all the prescriptions.[53] Another USA study showed that over 50% of 65 cancer therapies were prescribed *off-label* for the treatment of breast cancer.[63]

In addition, *Mellor et al* assessed 448 chemotherapy protocols for 82 medicines in an Australian oncology centre in 2008 and found that 42% of all protocols included *off-label* prescriptions, while at another Australian oncology centre it was found that 35% of all prescriptions were *off-label*, but 85% of patients were prescribed at least one medicine outside the scope of MA.[64,65]

2.6. Examples of *off-label* use of medicines in clinical practice

To understand better the pattern associated to the *off-label* practice, two complied tables with some of the most reported *off-label* indications in our literature research are presented.

In the first table, the most common *off-label* indications are grouped by pharmacological class and in the second one the uses are associate to specific medicines.

Table 9 António Vaz Carneiro grouped the most common off-label uses with regard to pharmacological classes [7]

Pharmacological Class	***Off-label* Uses**
Antiepileptics	Migraine, depression, neuropathic pain
Antipsychotic	Alzheimer, autism, dementia, ADHD
Antidepressants	Chronic pain, ADHD, bipolar disease
Antihistaminic	Cold, asthma, otitis, sleep induction
Antibiotics	Viral infections
Anxiolytics	Sedatives, sleep induction
Proton-pump inhibitor	Sporadic dyspepsia, indigestion, irritable colon syndrome
Beta-blockers	Migraine, arrhythmias, anxiety
Medicines for ADHD	Increase concentration and performance in patients without ADHD
Hypnotic medicines	Insomnia related to depression and anxiety
Narcotic analgesics	Mild, sporadic pain

Medicines that belong to the same pharmacological class can potentially have the similar effects on the same pathology. Thus, it is expected that this rational substantiates also the *off-label* prescription. It is clearly evident in the table above that psychiatry medicines assumes great relevance in this field.

Table 10 Common Off-label vs on-label uses associated to specific medicines

Therapeutic area /Medicine	***On-label* use (most common)**	***Off-Label* use (most common)**
Allergy		
Diphenhydramine	Antihistamine (Allergic rhinitis)	Chemotherapy-related emesis, insomnia[22]
Hematology, including Oncology		
Dabigatran	Anticoagulant	Venous thromboembolism prophylaxis after orthopedic surgery[7,22]
Doxorubicin	Soft tissue and osteogenic sarcomas, Hodgkin`s disease and non-Hodgkin`s lymphoma, acute leukaemia, carcinomas and neuroblastoma	Refractory multiple myeloma[22]
Rituximab	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, pemphigus vulgaris	Idiopathic thrombocytopenic purpura, Waldenström macroglobulinemia[22] inflammatory and auto-immune diseases[28,46]
Bevacizumab	Different types of advanced or metastatic cancer	Age-related macular degeneration[7,23]
Factor VII	Specific forms of haemophilia	Control bleeding in non-haemophiliac patients procoagulant in cardiac surgery, trauma and intracranial haemorrhage[7,37,66]
Rheumatology		
Etanercept	Psoriasis, psoriatic arthritis, ankylosing spondylitis	Behcet disease, sarcoidosis, pyoderma gangrenosum[67]
Indomethacin	Non-steroidal analgesic and anti-inflammatory	Pharmacologic closure of patent ductus arteriosus[22]
Osteoporosis		
Alendronate	Postmenopausal osteoporosis	Hypercalcemia of malignancy[22]
Infectious disease		
Linezolid	Nosocomial pneumonia, community acquired pneumonia, complicated skin and soft tissue infections	Infective endocarditis[22]
Sulfamethoxazole-trimethoprim	Respiratory, gastro-intestinal, genital and urinary tract infections	Sinusitis[22]
Quinine	Antimalarial	Nocturnal leg pain[68]
Erythromycin	Antimicrobial action	Gastroparesis[22]
Nephrology and Urology		
Erythropoietin	Anti-anaemic- symptomatic anaemia associated with chronic renal failure	Anemia of chronic diseases[22]
Furosemide (nebulized)	Diuretic	Dyspnea[22]
Sildenafil	Erectile dysfunction in men	Sexual dysfunction symptoms in women[22] pulmonary hypertension in children[22] increase the sexual performance in patients without sexual disfunction[7]

Therapeutic area /Medicine	***On-label* use (most common)**	***Off-Label* use (most common)**
Neurology and Psychiatry		
Gabapentin	Antiepileptic, peripheral neuropathic pain- epilepsy	Depression, migrine[7,68,69] bipolar disorder, diabetes, fibromyalgia, hiccups, hot flashes, restless leg syndrome[22,53]
Sodium Valproate	Anti-epileptic	Mania associated to bipolar disease[46]
Olanzapine	Antipsychotic primarily used to treat schizophrenia and bipolar disorder	Psychosis apart from schizophrenia[46]
Donepezil	Symptomatic treatment of mild to moderately severe Alzheimer's dementia	Frontotemporal dementia[22]
Betahistine	Vertigo, tinnitus and hearing loss associated with Ménière's syndrome	Benign positional vertigo[68]
Tricyclic antidepressants (Amtriptiline)	Anti-depressive, nocturnal enuresis	Bulemia, insomnia, irritable bowel syndrome, neuropathic and chronic pain symptoms[22,66,68] migraine[28]
Sertraline	Anti-depressive	Generalized anxiety disorder[68]
Paroxetine	Anti-depressive	Diabetic Neuropathy [68]
Venlafaxine	Anti-depressive	Fibromyalgia [68]
Mirtazapine	Anti-depressive	Sleep disorders[28]
Trazodone	Anti-depressive	Insomnia[22,28,68]
Topiramate	Antiepileptic	Depression, neuropathic pain, bipolar disease [7,68]
Aripiprazole	Antipsychotic (schizophrenia, manic episodes in bipolar disorder)	Alzheimer, dementia[7]
Risperidone	Antipsychotic (schizophrenia, manic episodes)	Alzheimer, dementia, eating disorders[7]
Atypical antipsychotics (risperidone, olanzapine, quetiapine)	Antipsychotic, Schizophrenia	Anxiety, dementia, eating disorders, obsessive-compulsive disorder, personality disorders, posttraumatic stress disorder, substance abuse[22] depression[69] sleep disorders[28]
Lamotrigine	Antiepileptic and Bipolar Disorder	Depression, mood stabilizer[7]
Tiagabine	Antiepileptic	Depression, mood stabilizer[7]
Citalopram	Depression and panic disorders	Alcoholism, fibromyalgia, irritable bowel syndrome, obsessive-compulsive disorder, pathologic gambling, stuttering[22] generalized anxiety disorder[68]
Modafinil	Wakefulness-promoting agent (excessive sleepiness associated with narcolepsy)	Attention increase[7] general fatigue and excessive daytime sleepiness or tiredness, difficulty concentrating, and cognitive impairment[66]

Therapeutic area /Medicine	***On-label* use (most common)**	***Off-Label* use (most common)**
Cardiology		
Acetylsalicylic acid	Pain, fever, rheumatic diseases, cardiovascular diseases (eg, acute myocardial infarction, previous myocardial infarction, angina pectoris, and previous cerebrovascular disease), history of a revascularization procedure (eg, coronary artery bypass grafting and carotid endarterectomy)	Prophylaxis for coronary disease in high-risk patients (diabetic), prevention of a first myocardial infarction in individuals at moderate or greater risk of coronary heart disease[15,22, 49] in diabetes for prophylaxis against cardiovascular disease[69] antithrombosis in atrial fibrillation, Kawaskai disease[22]
Nifedipine	Hypertension, prophylaxis of chronic stable angina pectoris	Tocolytic (labour inhibitor) [1]
Beta-Blockers (propranolol, nebivolol)	Anti-arrhythmic, antihypertensive cardiac arrhythmia, hypertension	Anxiety, social phobia, public speaking[22] Essential tremor [7]
Atenolol	Hypertension, angina pectoris, cardiac dysrhythmias, myocardial infarction	Migraine prophylaxis[22]
Dermatology		
Azathioprine	Immunosuppressant	Atopic dermatitis, pemphigus; psoriasis[22]
Biologic agents (eg, etanercept, infliximab, intravenous immunoglobulin, rituximab)	Immunosuppressant	Alopecia areata, atopic dermatitis, Behçet disease, dermatomyositis, hidradenitis suppurativa, pemphigoid, pityriasis, vasculitis[22]
Anaesthesiology		
Propofol	Sedative–hypnotic,'inducing' anaesthesia	Antipruritic related to surgical anesthesia[34] intracranial hypertension[22] postoperative nausea [22]
Volatile anaesthetics (eg. enflurane, isoflurane, halothane)	Anaesthesia	Status asthmaticus[22] intraoperative uterine contraction[22]
Lidocaine	Anaesthesia	Postherpetic neuralgia[22] lombalgy, muscular pain, elbow ténis pain[7]
Cetamin	Anaesthesia	Depression [28]
Isoflurane	Anaesthesia	Seizure, status epilepticus[22]
Gastroenterology		
Omeprazole	Duodenal ulcers, reflux oesophagitis	Reflux-related laryngitis[22]
Magnesium sulphate	Hypomagnesaemia	Premature labor[22]
Misoprostol	Duodenal ulcer and gastric ulcer	Treatment of missed and incomplete miscarriages, the induction of abortion, and cervical preparation before uterine instrumentation, induction of labour and postpartum haemorrhage prophylaxis and treatment labour / contractions induction[28,53]

Therapeutic area /Medicine	***On-label* use (most common)**	***Off-Label* use (most common)**
Immunology		
Tacrolimus	Prophylaxis of transplant rejection	Autoimmune diseases[69]
Pulmonary		
Montelukast	Anti-asthmatic	Chronic obstructive pulmonary disease[69]
Bosentan	Pulmonary hypertension	Raynaud disease, scleroderma[67]
Acetylcysteine	Mucolytic agent	Prevention of contrast nephrotoxicity[22]
Salbutamol	Anti-Asthmatic and bronchodilator	Chronic obstructive pulmonary disease, chronic cough [7] hyperkalemia[22]
Endocrinology		
Metformin	Antidiabetic	Polycystic ovary syndrome[23,69]
Dexamethasone	Disorders amenable to glucocorticoid therapy	Postoperative nausea[22]

The table above demonstrate that *off-label* uses extend to a range of therapeutic areas and classes of medicines. It englobes since older molecules (eg. Lidocaine, Magnesium sulphate) to the newer biological agents, which reveals that the *off-label* use is not confined to a specific type of treatment, thought, there are areas where this prescription is more expressive, as psychiatry, oncology, cardiology, respiratory and gastrointestinal. Consequently, the risks and costs associated to the medicines also differ. In generally, the newer, more expensive medicines, often associated to highest risk of side effects have a greater economic impact.[18]

It is important to note that depending on the country the situation of the indication could change (approve to unapproved or vice-versa). A medicine may have a different authorization status in different countries.

In all the examples reported, there was a need of exploring the potentiality of approved treatments for other indications, which was triggered by the similarity of the disease symptoms, mechanism of action and disease´s physiopathology.

2.7. Scientific Support behind *Off-label* Prescription

Various authors pointed out the scarcity of evidence support behind the *off-label* prescription.[62,68,70] According to some studies, more than two thirds of these prescriptions had no scientific evidence supporting them and just 30% of *off-label* practices were justified by strong scientific evidence**.**[14,15,23,70].

A survey of 150 million off-label prescriptions in the USfound that 73% had little or no scientific support, even when sources other than the product information were searched. [18]

However, and also in these previous studies, the context and methodologies influence the results. Additionally, it is important to understand the definition assigned to "Strong Evidence" by each author.

Radley *et al*, used the DRUGDEX [a] system to create a database of scientifically supported *off-label* indications. They considered an indication was to be scientifically supported if, according to DRUGDEX, its effectiveness has been shown in controlled trials or observed in clinical settings. All other indications that lacked FDA approval or that did not meet the criteria for having scientific support were considered to be *off-label* with little or no scientific support. In Table 10, the scientific support evidence associated to some therapeutic classes reported by the authors is presented. It is demonstrated that *off-label* prescription with limited or no scientific support was more common than supported *off-label* use in all the selected classes.[62]

[a] Recognized pharmaceutical compendium that describes the efficacy and scientific documentation for labelled and *off-label* uses of prescription medicines.

Table 11 Level of Scientific support of off-label prescription. Adapted from the study [62]

			***Off-label* use**	
			Strong scientific support	**Little or no scientific support**
Therapeutic Class	**Estimated No. of mentions in millions**	**% of *Off-label* mentions**	**No. of mentions in millions (%)**	**No. of mentions in millions (%)**
Cardiac therapies	9,5	46,0	3,8 (39)	5,8 (61)
Anticonvulsants	6,6	46,0	1,1 (17)	5,4 (83)
Anti-asthmatics	17,7	42,0	8,3 (47)	9,4 (53)
Psychiatric therapies	18,0	31,0	1,0 (6)	17,0 (94)
Antimicrobials	35,5	23,0	11,6 (33)	23,9 (67)
Analgesics	6,2	6,0	1,3 (21)	4,9 (79)

Another study in Canada also categorized the prevalence of *off-label* prescription taking into consideration the level of evidence. However, the author identified limitations to the study related to the compendium used to evaluate the level of evidence (methods used to classify evidence are not transparent and the evidence is not necessarily up-to-date). According to table below, excluding cardiovascular area, more than 80% *of off-label* use lacked strong scientific evidence.[68]

Table 12 Level of Scientific support of off-label prescription. Adapted from the study [68]

			Proportion of *Off-label* use by degree of scientific evidence (%)	
Drug American Hospital Formulary Service Class	**No. of prescriptions**	***Off-label* use, No. (%)**	**With strong evidence**	**Without strong evidence**
Central nervous system	58914	15491 (26,3)	18,2	81,8
Gastrointestinal	14237	1770 (12,4)	15,1	84,9
Anti-infective	21000	3599 (17,1)	4,6	95,4
Antineoplastic	234	28 (12,0)	0,0	100
Blood and coagulation	1328	23 (1,7)	0,0	100
Cardiovascular	70953	2313 (3,3)	58,8	41,2

Even taking into consideration the studies´ limitations, these numbers are extremely worrying as the potential for injury seems to be highest when there is a lack of a solid evidentiary basis.

3. LOOKING AT NATIONAL FRAMEWORKS

Member States have their own rules in place with regard to the prescription of medicines, including *off-label* prescribing, though this is not harmonized. In some countries provisions about *off-label* are included in the national law, while other countries address this question through good practice guidelines/professional recommendations or reimbursement decisions.[4,36] There are also EU countries as Portugal that do not have any specific regulation in force.

Observing what is being adopted can provide valuable information and orient the future actions. Therefore, a summary of the current practices is presented hereinafter.

For all cases, MAH should notify any suspected adverse reaction, avoid any promotional activity of the *off-label* use of the medicine and provide to the Agency any information related with this use that may have any impact on the recommendations.

Although different, the policy tools described below have similar purposes, namely: safer *off-label* use of medicines; better monitoring; knowledge improvement regarding efficacy and safety of this kind of use; ensure equitable access; create the opportunity to apply the results of research immediately; disseminate information on evidence-based medicine for improved patient care and provide guidance to prescribers.

Table 13 Countries where no specific regulation with regard to off-label use is in place

Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, Ireland, Malta, Portugal and Slovenia

No regulations or policy tools specifically on off-label use[4]

- Only general legislation to regulate the prescribing of medicines
- Issue should be dealt in the context of the prescriber-patient relationship rather than at the regulatory or healthcare system level (prescriber responsibility)
- Patients should be properly informed and provide consent
- No systems in place to identify *off-label* use

Table 14 Countries with specific legislation or related measures with regard to off-label use

France: ***Temporary Recommendations for Use (RTU)*** [4,5,12,16,27,71]

- RTU system is set up at the initiative of the Agence Nationale de Sécurité du Médicament (ANSM) which inform MAH about the need of RTU - specifies the indication and the posology.
- MAH has to provide all available data on the concerned indication, though pharmaceutical companies are not eligible for requesting RTUs .
- Prescription has to mention the RTU and physician has to inform the patient of the *off-label* use and of the potential benefits and risks associated.
- A medicine covered by RTU can be reimbursed by the national health insurance.
- Patients should be monitored through a protocol - MAH is obliged to set up a follow up of patients based on safety and efficacy information, real conditions of use, monitor prescriptions' adherence to the RTU (data sent regularly by the MAH to ANSM) - ANSM can modify, suspend or withdraw the RTU.
- Agreement signed between the ANSM and the MAH with a potential commitment to eventually file a further MA application.

Hungary: ***Permission request for off-label prescribing*** [4,8]

- *Off-label* use of any medicinal product is subject to specific, individual authorisation of the Health Technology Assessment Committee and the National Institute for Quality and Organisational Development in Healthcare and Medicines. Physicians need to apply for a permission (an application licence).
- Prescription authorised if: treatment of a patient with another authorized medicinal product is not possible or unsuccessful and for medicinal product with MA in Hungary or in another country. Once permission is granted, this will be published, and it is valid for patients in the same condition.
- For an *off-label* use covered by published permissions or by HCPs' protocols, a simplified application for permission may be submitted.
- *Off-label* use can be reimbursed on a case-by-case basis by the National Insurance fund.

Italy: Legal framework for off-label use National Law n. 94/98 (the so-called Di Bella law) and 648/96 national Law [4, 5,10]

- It is possible according to national Law n. 94/98, under the personal responsibility of the prescribing physician and in therapeutic areas with an unmet medical need and/or companies do not want to perform clinical trials for a specific indication (Ln.648/9). Patient consent is a precondition.[a]
- Prior checking (registration on a list) or a scientific validation (choice of physician literature-based) is required, including support of phase II completed study.
- In case of application of law 648/96 the *off-label* use is reimbursed. Law 79/2014 has introduced the possibility of reimbursement of *off-label* indications for which there are already alternatives on the market, as long as supported by robust scientific data (assessment of economic appropriateness). [b]

Spain: ***National Royal Decree No. 1015/2009*** [4,5,10,12]

- […] exceptional and only limited to those situations in which no approved alternatives exist.
- Physicians have to adequately justify the need for treatment and informed consent of the patient is required.
- Therapeutics committees of hospitals perform an evaluation of individual cases and the medical director must give authorization for each patient.
- Spanish Agency may establish therapeutic protocols and/or recommendations for the use (or not use) of medicines for conditions different to those authorised and inform the MAH about the recommendations of use and the suspected adverse reactions - authorisation from the medicine's agency is not needed.

Germany: ***Expert Commissions for off-label-use*** [4,5,10]

- Commissions for *off-label* use have been established within the national medicine's agency (Federal Institute for Medicines and Medical Devices, BfArM).
- Evaluate the current scientific knowledge about the *off-label* use of specific medicinal products for specific indications- evaluations may be solicited either by the Federal Ministry of Health or by the Federal Joint Committee (G-BA). *Off-label* evaluations need the consent of the respective MAH and can be reimbursed.

[a] However, the lack of obligation to systematic monitoring might be a weakness.

[b] This measure provoked a number of reactions from the EFPIA, according to which the wide authority of the Italian Agency and inclusion in the "648 list" of cheaper alternatives helps maintain this type of practice.

Greece: *Permission request for off-label use* [4,5]

- Ministerial decree is required for physicians to prescribe *off-label*-special cases and according to international bibliographic references.
- Reimbursement can be submitted by hospitals, the National Organisation for Health Policy Provision (EOPYY) and other Social Security Funds or if included in therapeutic protocols approved by the Central Committee of Health Council (KESY).

Netherlands: *Regulating through professional standards* [1,4,5]

- *Off-label* prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific use (Art n. 68 Medicines Act). […] if protocols or standards are still under development, the physician and the pharmacist are required to consult each other. Evaluation Board and the Dutch Healthcare Inspectorate evaluate if *off-label* use entails the requirements of existing scientific evidence and if the informed consent was obtained.
- HCPs need to register the indication on the reimbursement form when they prescribe a category of expensive medicines to patients (both *on* and *off-label* indications).

Lithuania: *Regulating how to put off-label use in practice* [4]

- Description of how to use products *off-label*, how the physicians should act in these situations, and what documents they need to complete. Officially, patients can be treated with a product that is not registered and also regulate its reimbursement.

Sweden: *Informed consent and Guidance for prescribers* [4]

- Any therapeutic intervention, (including *off-label* prescribing) should be based on scientific and clinical experience.
- Patient should be consulted and give consent (Patient safety legislation SFS 2010:659, Patient legislation SFS 2014:821).
- Medicines committees recommend follow up on prescribing patterns, and the Health and Social Care Inspectorate monitors *off-label* prescribing.

United Kingdom: *Prescribing hierarchy and Guidance for prescribers* [4,5,10,39]

- UK has a 'soft law', using a prescribing hierarchy: (1) use a licensed product, (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.
- Good practice in prescribing and managing medicines: sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy; take responsibility for prescribing the medicine; monitoring, and any follow up, record of all medicines prescribed and, justification not to follow common practice.
- Decision-making by prescribers, is generally done in accordance with authoritative clinical guidelines- National Institute for Health and Care Excellence (NICE).

USA:*FDA draft guidance and good reprint practices* [1,5,13,38]

- FDA does not have the jurisdiction to regulate the practice of medicine-physicians are free to prescribe medicines based on their own medical judgment ("practice of medicine exemption"). In 2015, the FDA released a draft guidance : patients will be eligible only when there is no other product that can diagnose, monitor or treat the patient's disease or condition and the patient cannot be enrolled in a clinical study testing it; the physician must determine that the probable risk associated to the medicine is not greater than the probable risk from the disease.
- "Right to try" law: terminally ill patients have the right to try experimental medicines that have passed at least the first of three phases of FDA testing (to determine safety) but have not obtained MA. FDA issued guidance on "good reprint practices" for distribution of scientific publications on *off-label* uses.
- *Off-label* medicines for specific diagnoses: DRUGDEX, AHFS Drug Information by the American Society of Health-Systems Pharmacists and USP (United States Pharmacopeia) Drug Information[a] - if a specific *off-label* use is listed in any of these three publications, Medicare accepts insurance coverage.

[a] In this case, indications are listed in one of three categories: accepted, unaccepted or acceptance not established. The category of accepted indications contains not only the indications that have been authorised by the FDA (or Health Canada, the competent authority of Canada), but also non-approved indications considered appropriate by USP Advisory Panels.

4. STRATEGIES TO REGULATE *OFF-LABEL* PRESCRIPTION

The existing *off-label* use framework shows that there is a need for a harmonized clear-cut guidance to manage properly this issue.

As resumed above, some countries have already specific guidance and legal provisions in force. However, none of the approaches is enough satisfactory and comprehensive, requiring significant improvement and update. To ensure access to high quality and safe medicines for EU population it is essential to seek a coordinated approach, applying the experience gathered from the different strategies already in force in the various member states.[10]

Possible measures to improve and harmonize the control and the safety of use *off-label* are presented below. Some of them are already implemented by individual countries and the others were proposed by different authors.

It is important that Member States look together into the opportunities and challenges inherent to each measure and try to define and implement a harmonized approach to achieve a better managing and control of *off-label* use of medicines. I believe that there is not a unique solution, considering all the complexity of this issue. Maybe a combination of "soft law/measures" can be more prudent than impose a rigid legislation. *Off-label* uses substantiates the field of exceptions and because of that defining general strict requirements could not only be a virtually impossible task but also compromise the patient -as the exception (individual clinical situation could benefit from a specific use that not fit in the average patients).

Table 15 Possible measures to manage off-label use of medicines

Granting the right to apply for MA to third party - Government/firm co-Financed trials[2,5,12,73]	
Opportunities	• The third party fulfil all legal requirements could obtain a MA - coalitions of not-for-profit research institutes, payers, authorities and patient. • In case of no interest from original MAH to perform the necessary trials (off-patent/ repurposed medicines). • Shifting the responsibility to generate safety and efficacy data to the government- publicly funded clinical trials can fill in current gaps and help improve knowledge about the benefit–risk balance of medicines in non-authorised uses. • Collaboration in evidence generation on the European level - foundation of research calls on a non-commercial, public health-driven basis - EU´s Framework Programme (which has an overall budget of €80 billion for 2014–2020 with prospects of increasing in the future). • Programmes that help enhance the capacity of non-profit organisations to conduct R&D- European Clinical Research Infrastructure Network (ECRIN), which provide assistance to academics and independent researchers to overcome barriers in the conduct of multicentre and international clinical trials. • Some Member states have already initiatives in force: Italian Medicines agency (AIFA) supports independent research on medicines - the programme was financed through an hoc fund set up by AIFA, to which pharmaceutical companies had to contribute with a percentage of their annual expenditure allocated to promotional initiatives aimed at physicians; Trial Programme from the Belgian Health Care Knowledge Centre (KCE), which supports research by non-commercial entities (programme focuses on comparative effectiveness trials and aims at improving patient care and the efficient use of healthcare resources and budget). • Public funding of clinical research and clinical trials has been found to be a good investment of public money and can have a significant impact on clinical practice.
Challenges	• Restrictions on who can apply for an MA extension for off-patent medicines-regulatory frameworks should be amended to allow this to be done by not-for-profit organisations and other non-commercial players. • Measures to promote the sharing of relevant data by industry to support MA extension applications by third parties. • Bridge the gap between research conducted by non-commercial actors on new medicines uses and the extension of the MA for these medicines. • Lack of clear communication channels between preclinical scientists and clinicians. • Sharing of information to health care professionals -open data and open access (including timely publication of clinical trial results in publicly available registries). • Absence of incentives for scientists because the successful translation of preclinical results into new treatments is not a key performance indicator for academia. • Limited budgets of the government for public funding of clinical trials- choices have to be made.

Information measures- Awareness campaigns for patients and HCPs[4,5,13,18,35]	
Opportunities	• Physicians report the necessity to be appropriately informed on the issue of *off-label* prescription. • Information campaigns conducted by different bodies, for example professional organisations, patient organisations, government, regulators or a combination. • Social security and public health authorities have many tools that they can use to share information with the health professionals. • Information to those who need it at the moment they need it: tailored to the needs of specific groups of HCPs is preferred, tailored to the need of the patient provided by HCPs. • Enhances the decision-making process between prescriber and patient -patients can get more evidence-based information to make an informed decision. • Example of model applied by FDA on the dissemination of reprints and other medical communications (outside of the package leaflet): statement that the use has not been approved; or has been rejected (summary of the basis of the rejection), summary about ongoing studies with the medicines in the *off-label* use, reprints of peer-reviewed studies of the medicine in that use and a summary of the results of these studies; statement about the eligibility of the use of the medicine for reimbursement; dosing information based on peer-reviewed papers and protocols of ongoing studies. • In the UK, evidence summaries: unlicensed and *off-label* medicines have been introduced by NICE- provide a summary and critical review of the best available evidence for selected *off-label* medicines that are considered to be of significance, aimed at supporting the decision-making.
Challenges	• The content of shared documents needs to be analysed with caution. • General campaigns for HCPs are not useful as needs for information may differ per country and per medical speciality. • If not appropriately oriented by a HCPs general information on *off-label* use might confuse patients.

Notification of *off-label* use through an infrastructure of electronic prescribing[4,5,74]	
Opportunities	• E-prescribing software could allow physicians to register and transmit the medicine indication in their prescriptions. • Information on the extent of *off-label* use – larger transparency in the true dimensions of this type of prescription. • Better information to the pharmacists which permits to improve efficiency of their work.

Challenges	• Physicians may experience the visibility as a liability threat. • The obligation to be more transparent should go hand in hand with measures ensuring that physicians feel confident about their prescription (eg. guidelines/recommendations on "justified" *off-label* use). • Physicians may be constrained to make the *off-label* use visible because the patient will sometimes no longer benefit from reimbursement. • Confidentiality of data needs to be taken into account, as some patients might not appreciate to have information on the indication transferred to the pharmacist. • Need of establishment of a system which permits to integrate the information.

Influencing the Reimbursement of *off-label* uses[4,5,36]	
Opportunities	• Making an authorised product available for *off-label* use by granting reimbursement for individual patient cases under the responsibility of HCP. • *Off-label* prescription should be validly seen as an acquired standard. • Only reimbursing in case of evidence (eg., resulting in inclusion in treatment guidelines)- the required scientific evidence to justify a reimbursement decision would be the evidence that would reasonably justify an extension/variation of the MA. • Additional requirements may apply, including the limitation to life-threatening or severe diseases or the absence of alternative options.
Challenges	• Allowing reimbursement of *off-label* use based in price -product is less expensive than its *on*-label competitor -endanger agreed European scientific standards, thus putting patients' safety at risk. • *Off-label* use is not the right platform to address high costs of medicines- cannot be applied for only financial considerations. • Absence of a risk-benefit profile – how to perform a decision of reimbursement without the necessary data?

Validation by Authority/Permission to prescribe *off-label* [4,13]	
Opportunities	• Increased access to medicines with an established risk-benefit analysis- the use is approved by a competent authority based on evaluation of available evidence. • Patient and public health safety is increased. • Improves the position of the prescriber in terms of liability. • Patients can access more evidence-based information to make an informed decision. • Better overview of the products prescribed *off-label* and of the patient groups treated. • Already implemented in Hungary.

Challenges	• Evaluation is like the market approval and may lead to a refusal -while this might be for the benefit of the whole population, it may be disadvantageous for individual patients. • The time lag before permission is granted– in case of severe diseases/urgent action may have a negative impact on the patient -possible exemption of some types of products/ *off-label* uses from permission applications. • Administrative burden for HCPs to ask for permission and for the authorities to process the approval requests. • Medicines entering into "permitted lists" just based on economic reasons. • This measure would circumvent the need for a MA.

Encouraging requests for extension of indications by using new models such as RTU[4, 13,12,18,71]	
Opportunities	• Legal framework to issue temporary recommendations for *off-label* use- regulatory agencies play a proactive role. • Monitorization of patients through a protocol- better overview of indications for which medical products are prescribed and improvement of the knowledge regarding efficacy and safety of *off- label* use. • Compromise to collect safety and efficacy data and file an MA extension (pharmaceutical companies). • HCPs liability with this option is similar to authorized products. • Safer use of prescribed medicines by looking objectively at their therapeutic benefit with respect to the risks to which they expose patients- HCPs can prescribe a product for which a risk-benefit analysis is established (evaluated by an authority). • Patients can access more evidence-based information to make an informed decision. • Ensure equitable access and the highest possible level of safety of use for medicines outside of existing regulatory frameworks (MAs, clinical trials). • Already implemented in France.
Challenges	• Evaluation is like the market approval and may lead to a refusal -while this might be for the benefit of the whole population, it may be disadvantageous for individual patients. • The time lag before permission is granted– in case of severe diseases/urgent action may have a negative impact on the patient -possible exemption of some types of products/*off-label* uses from permission applications. • Administrative burden for HCPs and companies -there is reluctance of some MAHs and physicians to implement the follow-up of patients. • Allowing *off-label* use when there are alternatives on the market -reimbursed by the national health insurance also if there is an on-label alternative (as happen in France). • The validity-period may be short for collecting data for a future MA application file (in France 3 years are granted). • RTUs will only concern a small portion of medicines.

Providing guidance at EU level (Treatment guidelines) [4,13,30,36]	
Opportunities	• Guidance at EU level could provide a common ground for national treatment guidelines in EU Member States- guidance on what elements could be included in national treatment guidelines on *off-label* use (eg. informed consent, various levels of evidence, information for the patient, monitoring, patient involvement in preparing guidelines) and how guidelines could be developed • Harmonized positioning of *off-label* use in relation to EU legislation on MA. • The evidence on which guidelines are based is evaluated by their professional organisation or a designated guideline commission- provides insights in the risk-benefit ratio of medicines • The evidence is easier to include in guidelines than in the SmPC, which are owned by the MAHs. • Strengthens the position of patients -HCPs get guidance in what treatment is generally best for patients with a specific disease including *off-label* options- prescribers and patients can make an informed decision. • Guide for clinicians, policymakers and funders of health care in evaluating the appropriateness of medicines proposed for *off-label* use. • Netherlands, *off-label* prescription is allowed: if the relevant professional body has developed protocols or professional standards with regard to that specific use. • Harmonized information - on 8 April 2017, the Standing Committee of European Doctors sets out some best practice for prescribing a product *off-label*.[a] • Coalition of European organisations- GOLUP principles serve to create a framework to ensure that the interests of patients, prescribers, pharmacists and the public at large are protected -the signatories of this declaration call on the EMA and other national regulatory bodies to adopt strict guidelines to support HCPs in ensuring safe medicines therapy.
Challenges	• Choices for *off-label* use remain the responsibility of the prescriber as guidelines are not compulsory. • Guidelines are created based on average information-could not fit a specific patient /situation. • The context of *off-label* use differs Member States- treatment guidelines should be at a national level, although harmonization is required.

[a] CPM Policy on *Off-label* use of Medicinal Products (CPME/2017/006/Final), https://www.cpme.eu/cpme-policy-on-off-label-use-of-medicinal-products/

Use of evidence other than industry-based Randomized Clinical Trials for MAHs to support the application of an indication extension [4,7–9,13,17,60,75–79]	
Opportunities	• Use of evidence from patient registries or pharmacovigilance data- enable to monitor efficacy and adverse effects of *off-label* use. • Emergence of "big data," randomized registry trials, and other modes of knowledge production in medicine • Real-world evidence, collected by industry could serve as the basis on which the regulator decides whether or not to grant authorisation for an indication. • Increase the knowledge on the risk-benefit balance of medicines -increases the scientific profile of the product. • These data are especially useful if clinical trials are hard to carried out. • EMA and Heads of Medicines Agency (HMA) have established a joint task force to investigate the potential role of 'big data' in the context of medicines development and regulation in the EU • The rise of personalized medicine might make it more difficult to defend gold standards (randomized clinical trials) in diagnostic and therapeutic practice- personalized medicine refocuses clinical attention away from the "typical" patients analysed by clinical trials and onto the idiosyncrasies, genetic of individual patients. • Post-authorisation safety/efficacy studies- observational studies (eg., cohort or case–control studies) from post-marketing surveillance can provide the necessary data. • Medicine utilization databases may be helpful in monitoring *off-label* use of medicines- information of the age range of patients, the duration of therapy, concomitant medication used, and doses prescribed. • Electronical healthcare databases that contain information both on medicine use data and medical diagnoses can also be useful for identifying trends in *off-label* use- central registry for HCPs to log in and compile data regarding their *off-label* use of medicines might be useful to harmonize the information (efficacy and safety) for off-patent medicinal products. • Centralization of information- EMA could play a role in the elaboration of a central population-specific database (as already done for safety issues – EudraVigilence). • The concept paper Extrapolation of efficacy and safety in medicine development released by EMA could be applied in case of *off-label* use : extending information and conclusions available from studies in one or more subgroups of the patient population, or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product- reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product- Extrapolation i) between population subsets ii) between disease subtypes or stages, different diseases, symptoms; iii) between medicines, within and between classes; iv) from animal studies to humans; v) from healthy volunteers to patients.

Challenges	• Databases do not typically contain information on indications for use • Clinical trials are the golden standard and the most suitable studies for medicine risk-benefit assessments: evidence from other sources is usually less solid- internal and external validity could be hard to define and achieve. • Personal data protection -databases should be anonymous and not contain patient or practitioner identification as this might hamper prescribers to register information. • Definition of quality standards of data to meet in order to be acceptable as evidence in the MA process - these standards should be developed at EU level in order to comply with the legal framework of the Europe. • The administrative burden for HCPs associated to the information register. • Integration of information -there is still no central, shared database- 80% of health data is invisible to current systems because it is unstructured.

Specialised scientific committees for *off-label* use[27]	
Opportunities	• Composed of representatives from the Regulatory Authorities, regional pharmacovigilance centres, General for Health, Directorate for Social Security, and the National Health Insurance Fund and HCPs experts. • Monitoring of *off-label* prescriptions by consulting and analysing existing databases and international scientific literature -implementation of mechanisms to monitor the *off-label* prescriptions in public health institutions. • Better control and evaluation of *off-label* use can be achieved. • Drafting of pharmaco-epidemiological-economic protocols. • Research into mathematical models on population pharmacokinetics for risk population, such as the elderly patients or pregnant women. • Education programs and communication towards the various health actors. • Already implemented in Germany.
Challenges	• Regulatory Agencies in general prefer to not be involved- as this is not within the scope of their responsibility. • High number of situations to be covered.

5. DISCUSSION

After presenting the current framework of *off-label* use of medicines and various aspects associated to this practice, I would like to expose some personal reflections of more controversial issues as well as possible future strategies in this field.

There is absolutely no doubt that *off-label* use of medicines is an essential and inevitable option for the treatment of patients around the world. Nevertheless, *off-label* practice poses a range of quite different challenges but also raises a lot of opportunities in the therapeutic field, as summarized below.

Table 16- Opportunities and Challenges in Off-label use

Opportunities	Challenges
Unavailability of medicines/ therapeutic option fails- patients demand new approach or new treatment.[49] Therapeutic options might get restricted without off-label prescribing in some patient population/ clinical situations.[7,28,37,49]	Raises key concerns about risks to patients - *off-label* uses are not given the same degree of scientific scrutiny as labelled indications (absence of authority evaluation/approval).[23,49] No guarantee of its scientific validity-the level of evidence is not as robust as for labelled claims.[31,70]
Earlier use of medicines, considering the long period of the authorisation process- special important in severe and critical clinical situations.[7]	Evidence that the incidence of adverse medicine reactions is higher for *off-label* medicines than licensed preparations- may be associated with an increase in medication errors.[22,28,80]
Freedom to physicians to apply new therapeutic options based on the latest evidence- physicians can generate evidence prior to the official approval by the authority.[7,49] Pathway to innovation in clinical practice- discover of new therapeutic indications.[7,23]	Costs to the health care system- Possible Increase of health expenditure.[7, 23] We cannot be sure of the cost-effectiveness of these medicines.[37] Liability of physicians is increased.[7] Low level of adverse events report can occult safety concerns.[7] Can undermine the regulatory system of medicines and clinical research – diminution of the incentive to Pharmaceutical Industry to conduct clinical trials for new indications. [7,28,37]

It is interesting to observe that a robust normative structure has been created and improved over the years in order to guarantee that medicines are properly evaluated before being placed on the market. However, the appearance of *off-label* uses suggests a weak point in today´s regulation and raises many questions about the risk, ethics, and legality of this type of practice.

Off-label use lacks rigorous and scientific evaluation and may pose enormous unknown risks to the health and safety of the public. Contrary to *on-label* use, *off-label* treatments have not been subject to randomised clinical trials and therefore the evidence with respect to the risk-benefit ratio is not of the same quality as that included in the dossier. This increases the uncertainty on efficacy as well as the risk for toxicity and other side effects.

I strongly agree with Schoonderbeek *et* al[1] in that "*Off-label* use is here to stay. As long as there is no complete overlap between the interests and drivers in the regulatory world and the world of medical practice, *off-label* treatment will be necessary."

Although some initiatives have been triggered to bring these two realities closer (e.g. *Eudravigilance*, Post-authorisation Studies, Adaptative Pathways), science and clinical practice are much faster than the regulatory approval processes and consequently it will probably be impossible to reach a complete alignment.

Despite being aware that this is a widespread practice, it is also generally accepted that it should be exceptional and limited to some situations (no suitable authorised alternatives available). This practice should be driven first and foremost by the need to ensure best patient care, recognizing their autonomy and respect by their dignity. Prescribing *off-label* medicines shifts the patient-physician relationship: whereas it can potentially emphasise the paternalistic attitude of physicians, it can also, on the other hand, strengthen patients' autonomy since the necessity for consent requires a well-informed description of the benefits as well as the risks. In this regard, I believe that we still have a long way to go until we can assure that patients are all informed correctly whenever an *off-label* prescription is used.

The high percentages reported for *off-label* prescription (please refer to section 2.5.) suggests this kind of prescription is relatively common practice in some clinical areas.

By trivializing the *off-label* use, the efficiency and purpose of the regulatory system and particularly of medicine labelling can be at stake. Additionally, the absence of an efficient control of this type of prescription suggests the reported prevalence is an underestimation.

The identification of *off-label* prescription is a very complex task. For it to be efficient, we must be able to cross reference the available independent databases (such as pharmacovigilance database, medicalized information system program, hospital medicine formularies, sales data and data from market surveys).[27]

Monitoring is crucial, not only to characterise the real scenario and help define strategies, but also to gather clinical evidence. Nowadays, the access and implementation of technologies in the health sector could facilitate this task, although a lot of barriers need to be overcame. Reinforcement of obligatory *off-label* reporting is expected to be hard to establish: the administrative burden still associated to the data register, the liability issues (increased visibility), the new data protection legislation and the unstructured databases are some examples. The centralization and standardization of criteria in data collection is indispensable to facilitate the analysis and conversion into scientifically validated information. Otherwise, this data would have no value.

As shown by the examples in section 2.6, there is a tendency to use medicines that belong to the same pharmacological class to treat the same pathology, based on the fact that they can potentially have comparable effects. For future work in this field, it would be interesting to realize an extensive analysis of medicines pharmacology and its influence in off-label patterns/choices and repurposing medicines.

Another point discussed in section 2.7. of this work is the level of scientific support associated to *off-label* prescription. The high number of these prescriptions with a low level of scientific support increases their safety risk.

Patient safety is a central concern in the medical field. In *off-labe*l prescription, even stronger emphasis should be given to this point. How can we assure the safety of a treatment that does not have a formally established risk-benefit profile? The level of appropriateness of *off-label* is also questionable, as this type of prescription should only be considered in case of being the best available option to a specific situation. Uniformized requirements in this evaluation have to be defined. In scientific literature, the terms

"appropriate" and "inappropriate" *off-label* use are often discussed but the specific criteria of what constitutes each is somewhat subjective and can vary among the authors.

Although it is clear that the *off-label* prescription is a physician's decision, the way in which the decision-making process is managed in the majority of the situations is both surprising and concerning. Whereas in a hospital setting the decision has to pass through the scrutiny of ethics and pharmacotherapeutic committees, in an outpatient setting, it probably depends only on the prescriber individual evaluation.

One might argue that we are going backwards when the clinical practice was based on deductive reasoning related to physiopathology and clinical experience, superseding the evidence-based medicine.

Physicians are technically able to diagnose and define a therapeutic strategy, but are they prepare to perform a risk-benefit analysis of a non-approved use?

In the case of *on-label* use, safety and efficacy evaluation is performed by committees of experts considering the compliance with pre-defined regulatory requirements and based on scientific validated data – clinical trials. Therefore, it can be concluded that to make a sustained decision on *off-label* prescription 3 aspects should go together- relevant data/evidence, establishment of technical requirements and evaluation by experts. In the scenario of non-approved uses, if some prerequisites were established, physicians will probably be able to decide better. The following points should be discussed:

- There are different levels of evidence (peer-reviewed publications, practical experience, standard treatment guidelines or medicine compendia): what would be the acceptable evidence to guarantee the expected level of efficacy and safety? In which sources of information should physicians base their decisions? It is important that HCPs have access to all available information when making a rational choice to prescribe *off-label*.

- Defining general guidance/requirements to assure a high level of rigour in the prescription decision. This not only better protects patients against safety concerns but also the prescribers regarding liability issues. It will also allow for some uniformization among the requirements that need to be fulfilled. The aforementioned GOLUP declaration is a first step towards this.

- Joint responsibility thought multidisciplinary expert groups or committees.

In my opinion, a way of addressing the above points is through "soft laws". Creation of EU guidelines as referred in section 4., with general guidance (levels of evidence, patient information, monitoring) would allow for harmonization in *off-label* prescription criteria. Furthermore, clinical recommendations on specific pathologies can be developed at a national level. With clinical recommendations, prescribers would base their decisions in pre-validated/peer-reviewed information and not only on their individual judgement. These recommendations should also reflect the most recent clinical evidence and the possible risk-benefit and cost-effectiveness balance. The benefits that can arise from this are obvious. This kind of approach will contribute to equity and will harmonize clinical practice. However, recommendations should be systematically reviewed as new research evidence becomes available and to ensure methodological consistency and transparency.

Although clinical recommendations cannot cover all possible circumstances and the individual complexity of each patient, they can provide a guidance in case of predictable and expected situations (diseases without approved treatment, specific patients' groups), allowing for a safer and more homogeneous medical supply for the patients concerned. Obviously, these recommendations should not replace the medical evaluation and they are not mandatory- the physician may consider other possible approaches depending on the situation. It is critical to strike the right balance between guidance/support and flexibility/choice/ autonomy for the prescriber.

If it is true that some guidance on this issue will bring tremendous benefits, it is also true that a rigid regulation in this field can be disadvantageous for the individual patient. For instance, the risk could overcome the benefits based on the general available evidence, and therefore not be considered in clinical recommendations. However, this risk could be acceptable for a specific patient.

The recommendations/guidelines can also help physicians handle the associated ethical and legal issues and protect them in terms of liability. In fact, the person most exposed to any negligence claim from patients as a result of *off-label* use is the prescriber. Thought accountable for their treatment decisions, in this kind of prescribing, their

responsibilities are enhanced especially in situations of an adverse event, poor clinical outcome and lack of proper documentation to support the decision.[9,14–16,18,28]

As a pharmacist, I must comment on the difficult position in which *off-label* prescribing places us. The pharmacists are required to evaluate/validate physicians' prescription orders to ensure that prescribed medicines are appropriate, prior to dispensing them. However, accessing basic patient clinical information is crucial to performed this validation. Routinely, pharmacists have their responsibility hampered given the scarcity of information available especially in the community settings. In many countries, pharmacists do not know for which indication the medicine has been prescribed, neither does the Social Security that reimburses it.[4,81]

One of the measures proposed in section 4. is the inclusion of therapeutic indication in the prescription, which will at least facilitate the pharmacists work. Also, the shared computerized patient file with rationale (eg., clinical evidence) on which the *off-label* medicine is being prescribed, would help pharmacists to fulfil their responsibilities. Fortunately, electronic prescribing is now routinely used, both inside hospitals and in ambulatory context and could serve as a platform for allowing communication between the prescriber and the pharmacist.

A recent article [74] analysing the benefits of incorporating medication indications into the prescribing process, suggests that the inclusion of this information will improve patient safety (better identification of prescription errors). Furthermore, it reduces the need for the pharmacist to contact the prescriber for missing information and identifies whether a prescription is for labelled versus *off-label* indications. The software behind such a system could also support physicians in their clinical decisions which would be advantageous in a busy practice setting and also alert them for the non-approved uses.[15] However, there are numerous barriers and complexities to successful implementation and, despite national and international efforts, little progress has been made to incorporate indications into the prescribing process as a standard.[74]

In a hospital setting, the pharmacist can have a more relevant role in the *off-label* use: not only do they integrate the pharmacotherapeutic committees where these issues are

discussed but also have a direct route of communication with physicians and easier access to relevant clinical information.

In order reduce the extent of *off-label* prescription, it is crucial to analyse and understand its drivers and define strategies accordingly.

As I work in the regulatory area, I would like to further explore the reasons associated to the regulatory framework that could motivate *off-label* uses.

Regulatory system should protect as many patients as possible, by enabling physicians to prescribe well-tested medicines to treat their patients. Incentives like the Paediatric and Orphan Medicines Regulations and the exclusivity extra year market protection have been created to incorporate more applications of medicines in the authorised domain (please refer to section 2.4.2.).

Nonetheless, pharmaceutical companies may not be willing to develop new indications. Several barriers that hinder the authorisation of new indications have been mentioned:

- In contrast to the development of new molecules, the current legal infrastructure of medicine patents and regulatory exclusivity periods does not effectively promote the development of new indications for existing medicines. The business model of the pharmaceutical industry revolves around patent rights and exclusivity periods. Consequently, these companies often stop testing medicines for new indications long before the patent term expires because the necessary clinical trials for a new indication take many years to complete and revenues for the new indication may not be worth the expense and effort of obtaining an extra indication approval.[5,15,22] Even though the new indications have the advantage of starting with a phase II /phase III trial which saves almost 40% of the costs of clinical testing, the costs are still large and can run between €10 million to €47 million for a phase III trial.[29,82]

- Patents for new indications of an existing medicinal product do not protect against generic competition. Once generics enter the market, patients will use the low-cost

generics regardless of whether they are taking the medicine for an old or new indication. Since physicians do not specify the indications in their prescriptions to pharmaceutical companies, these rarely have access to the information needed to enforce new patents use if generics are available. As such, pharmaceutical companies will have no incentives to invest in the development of new indications for 'old' medicines.[1,5,29] Considering what was stated above, the pharmaceutical companies will only seek approval for a new indication in cases where they can recover their R&D investment and have a profit margin. This is unlikely to happen for a medicine that is already on the market.

- Because the clinical development process required for demonstrating the efficacy and safety of a new indication for an already approved medicine is usually long and laborious, its cost might simply not be worth since *off-label* sales will continue without this investment anyway. More specifically, for the already off-patent products, generic competition and/or low medicinal product price will have a negative impact on the return for investments of new indications, as the (generic) competitor will also be benefited.[1,4,5,13]
- Although in theory *off-label* use is not reimbursed, in practice non-approved uses are already a source of income for pharmaceutical companies since it is often possible to bill them as *on-label* product.[5]

Questions can be raised about the effectiveness of the regulatory system with respect to the development of important secondary applications of medicines, and it is clearly evident that the generalization of *off-label* uses hampers their conversion into *on-label*.

Additionally, conducting expensive clinical trials that could produce non-supportive evidence is a risk that few are willing to take. Here, the monitorisation of programs as RTU can help gather evidence and predict the results of clinical trials.

Another aspect that should be underlined is the process of product information (label) update. This is subject to the submission of variations by the MAH and to further evaluation/approval by the authorities. Therefore, the efficacy and safety information gathered in daily medical practice is not automatically included and could take some time

to be integrated in the SmPC. Thus, there is an evident limitation in the "labelling process", which prevents a rapid access to effective treatments. It is necessary to adopt efficient methods to update the product information according to the scientific evidence in a quicker way.

Given the complexities involved, conflicts of interests can be raised. If we have scientific evidence that supports the *off-label* use, is it acceptable that we don't include it in the labelling? On the other hand, the current regulatory process of labelling update is a prerequisite to guarantee the patients safety. Moreover, the addition of new indications to the MA conditions and consequently of product information has to be initiated by the MAH and as we have just seen there is a lack of interest in converting *off-label* into *on-label* in the majority of situations.[7] Given the high costs of generating clinical information, it is possible that regulation may have the perverse effect of lowering the amount of information generated as the MAH may choose not to seek new uses approval.[29] Therefore, if it is not feasible to investigate a specific use for the MAH, this use will be unapproved and prescribed *off-label*. That is why option of granting a third party the right to apply for MA is starting to be considered (please refer to section 4.).

According to Lenk and Duttge, extensive *off-label* uses could be seen as a sign of a regulatory system which is overly rigid.[16] Even though I can understand that the rigorous requirements associated to evidence-based medicine and MA approval process can hinder the indications approval in some way, these are also needed to guarantee the patients safety. The complexity associated with this is huge: regulation must balance the benefits of information generation, safety, and efficacy, with the resource costs and implications of a delayed access and fewer products available.[29]

In my opinion, regulatory authorities can have an important role in ensuring equitable access and the highest possible level of safety of use for medicines outside the existing regulatory frameworks. Even though regulatory authorities cannot interfere with medical prescription and are understandably only willing to make statements regarding purposely evaluated (*on-label*) medicines or could otherwise see their mission compromised, they could develop measures beyond regulating the promotion activities such as, for instance, to optimise the collection of data on *off-label* uses for medicine

monitoring purposes and issue specific recommendations (synthesizing evidence/emanating reports).[12] Approaches like post-authorisation studies, could be applied in order to gain knowledge about medicines in a more rapid and efficient way (where *off-label* use is included), improving post-marketing medicine evaluation.

In the monitoring field, the Pharmacovigilance Directive introduces the collection of adverse reactions associated to *off-label*. Despite the importance of monitoring the safety of medicines in an *off-label* setting, there are many challenges that this situation presents. Firstly, spontaneous reports do not always contain the indication for use or other details that would allow one to determine that the medicine was used in a manner not consistent with the product's label. Secondly, the identification of an adverse medicine reaction in the *off-label* setting does not necessarily mean that this reaction is limited to that use. [8,15] Thus, it is difficult to determine with precision the prevalence of adverse effects related to this practice.

There is also a need to clarify the handling of *off-label* use cases which are not associated with the occurrence of suspected adverse reactions.[42] The lack of clarity in the Directive, GVP Good Pharmacovigilance Practice (GVP) and Q&A documents have resulted in some pharmacovigilance Inspectors and MAHs interpreting this to mean that MAHs should be collecting all individual cases of *off-label* use regardless of their association with an adverse reaction. In many instances MAH have included these on the safety database for lack of any other suitable repository.[42]

MAHs should be aware of how their product is used in practice and present information of *off-label* use in PSURs and risk management plans, if applicable. It is important to note that an extended description of *off-label* uses can change the risk-benefit ratio and subsequently impact on the MA.[42] However, there is an apparent conflict in the collection of information regarding this type of use. On one hand, training the sales staff for the effect would help to collect information more efficiently. On the other hand, there is a very fine line between that practice and the active promotion of *off-label* use, which is strictly prohibited.

Central to this debate is not only the information itself but also the regulations involved in shaping what information to gather and the conditions under which it should be made available to the public.[29]

It is understandable that promoting a non-approved use raises a lot of questions. However, the information to prescribers could improve their knowledge and contribute to a better and safer non-approved use. For this to be feasible, control tools should be available to avoid the increase of this practice in inappropriate situations. It is important to define which informational communication on *off-label* use cold be considered outside the scope of medicines promotion. The challenge is to strike the balance that best protects patients.

As has already been mentioned, the USA has a more permissive approach, allowing the dissemination of available new evidence on non-approved uses to prescribers. We should analyse this practice and try to understand if it has increased *off-label* prescriptions or if it has allowed a safer use of medicines prescribed *off-label.*

The role of innovation associated to *off-label* prescription in clinical practice is undeniable. It offers patients and physicians earlier access to potentially valuable medications and allows physicians to adopt new practices based on emerging evidence when no approved alternatives exist or approved treatments are unsuccessful.

As already discussed, the *off-label* monitoring is essential in many ways. Not only is it vital in terms of innovation and knowledge gathering, but it is also essential for registering the associated outcomes and preventing the information from being otherwise lost in the physicians´ office and having no further use. Data collection should not be a burdensome obligation but a new opportunity to improve the clinical practice.[33]

In the academic literature there is a tendency to report only positive experiences with *off-label* products rather than recording negative outcomes which introduces a bias. Routinely collected data may be difficult to publish without formal prospective ethical review, so the creation of explicit research registries to chart patient outcomes can be a suitable solution.[36]

As described by Goldenberg “We are in the midst of an evolution from rigorous data collection performed solely at research centres to data collection from clinical

encounters performed at physicians' offices. Each touchpoint in health care results in information recorded by different operators at different locations and in different formats. Recording occurs at various locations in the office, hospital, and at remote locations. Entry occurs in different formats such as text, numbers, and pictures. Information may be highly structured when entered through predetermined checklists or unstructured when entered as free text. With all of this information, it is difficult to determine the most meaningful data to collect."[33] By 2020, 2.314 BN gigabytes of healthcare data will be generated.[79]

Digital health is a reality today and we must be prepared to use data effectively to improve health information exchange, decision making and policy development, consumer and business outcomes, and development of products and services.[83] Moreover, the trend towards a more personalised medicine calls for the use of real-world evidence data.

In recent years, the conditions and responsibilities in some countries were defined through guidance and legal changes (please refer to section 3). However, in most European countries there is still a lack of specific rules for *off-label* prescribing.[10] The *Study on off-label use of medicinal products in the European Union*, was extremely important to expose (from a factual perspective) the current situation across Europe.

After its publication, the involved stakeholders were apprehensive to know how the EC would respond to the questions raised, and whether new legislation or guidance should be published. However, until now, no measures have been taken, which has disappointed some sectors, particularly the pharmaceutical companies. In particular, the lack of consideration given to *off-label* prescribing in the context of licensed alternatives and the promotion of *off-label* prescriptions for purely financial reasons supported by some EU authorities (France and Italy), reflects uncertainty in this area and highlights an urgent need for clarification at EU level.[13]

The economic factor cannot be the most important element in decisions about reimbursement and hospital funding. If the payers increasingly question the need to pay for products that are not proven to be safety and effective, how can this situation be accepted and managed?

On the other hand, it is worth mentioning that *off-label* use can make a negative contribution, especially in case of newer, more expensive medicines, often associated to greatest risk of side effects (please see section 2.6 for common examples of medicines used *off-label*).[18]

This kind of approach disrespects the protection of pharmaceutical innovation. The possible immediate savings obtained by the change to *off-label* medicines could compromise the I&D investment in the long-term.

6. CONCLUSION

The reasons and the consequences of using a medicine outside the approved conditions are diverse and complex. Thus, it is tremendously difficult to find a general solution to address this practice.

The added value that *off-label* prescriptions bring is antagonised by the high risk this practice represents since the safety and efficacy of an *off-label* medicine have not been confirmed.

Considering the several implications of *off-label* use at the patient level, HCPs level (e.g., liability issues), and to public health budgets, it is important to discuss the regulation of this practice. This should be driven by the need to protect people's health, especially regarding data collection, monitoring and the implementation of possible measures to facilitate the registration of *off-label* uses and to support appropriate prescribing. It can be concluded that only a combination of various strategies will likely be able to decrease the wide-spread *off-label* use.

Balancing the expectations of the different stakeholders could be very challenging:

-physicians wish to have the freedom to prescribe the medicine that better serves the patient's specific needs regardless of the label, but would also like to have more supportive guidance in their decisions;

-pharmaceutical companies seeks to enlarge their market, ensure revenues and sustain medicine development;

- patients want access to safe and effective medicines which are also affordable;

-payers want to pay for medicines with proven favourable risk-benefit evidence;

-regulatory authorities aim to provide a system that assures high-quality medicines and equitable access.

It is critical to stipulate the responsibilities of all parties participating in this therapeutic approach, and to ensure more cooperation and flexibility in finding new synergies between the concerned stakeholders.

Collaborative efforts among EU Member States are needed to increase the understanding of the extent of *off-label* use, and to identify critical areas where an urgent intervention is needed. Member States should exchange information and learn from each other's experience in regulating the *off-label* use of medicines. Therefore, a discussion should be initiated at the European level to address which measures could be adopted to improve the current *off-label* medicine use situation. The EC and regulatory networks, including the HMA, have an important role to play by promoting and enabling these discussions.

The current EU situation of *off-label* use is unsatisfactory and a harmonized approach would presumably be of even greater value to ensure access to high-quality and safer medicines.

The *off-label* use of medicines cannot be ignored or overlooked. The lack of normative frameworks at this level not only increases health inequalities and safety risks but it may also facilitate this kind of practice by exploring areas of ambiguity where policy is permissive or undefined.

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