Off-Label Use of Medicines – General Aspects, Challenges and Strategies

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LIST OF ABBREVATIONS

ADR	Adverse Drug Reactions
AIDS	Acquired Immune Deficiency Syndrome
AMG	German Medicine Act
Afssaps	French Agency for the Safety of Health Products, predecessor of ANSM
ANSM	French National Agency for the Safety of Medicinal and Healthcare Products
art.	article
ATU	Temporary Authorisation for Use (*Authorisation temporaire d'Utilisation)*
BfArM	German Federal Institute for Drugs and Medical Devices
BSG	Federal Social Court *(Bundessozialgericht)*
BVerfG	Federal Constitutional Court *(Bundesverfassungsgericht)*
CEPS	French Economic Committee on Health Products
CJEU	Court of Justice of the European Union
CSP	French Public Health Code
CSS	French Social Security Code
Dir.	Directive
EC	European Commision
EFPIA	European Federation of Pharmaceutical Industries and Associations
e.g.	for example *(exempli gratia)*
EMA	European Medicines Agency
et seq.	and the following *(et sequens)*
EU	European Union
FDA	Food and Drug Administration
G-BA	Federal Joint Committee *(Gemeinsamer Bundesausschuss)*
GVP	Good Pharmacovigilance Practice
HAS	French National Authority for Health *(Haute Autorité de Santé)*
HCP	Health Care Professionals
ICSR	Individual Case Safety Report (ICSR)
INCA	French Cancer Institute *(Institut National du Cancer)*

MA	Marketing Authorization
MAH	Marketing Authorization Holder
MS	Member State
NO	Number
PASS	Post-authorization Safety Studies
PD	Pharmacodynamics
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PTT	Temporary Protocol of Treatment *(Protocole Thérapeutique Temporaire)*
PUMA	Paediatric Use Marketing Authorisation
RADAR	Research on Adverse Drug events And Reports
Reg.	Regulation
RTU	Recommendation of Temporary Use (*Recommendation Temporaire* d'Utilisation*)*
SGB V	Social Insurance Code V *(Sozialgesetzbuch V)*
SPC	Supplementary Protection Certificate
SSRI	Selective Serotonin Re-uptake Inhibitors
SmPC	Summary of Products Characteristics
UK	United Kingdom
UNCAM	The Federation of National Health Insurance Funds (*Union nationale des caisses d'assurance maladie)*
UR	Use recommendation
U.S.	United States
WHO	World Health Organization
WIdO	*Wissenschaftliches Institut der AOK*

1. INTRODUCTION

To safeguard patient safety any medicine intended for marketing in the European Union (EU) must undergo a rigorous approval process. This includes an assessment of quality, safety and efficacy of the medicine for the intended use in the population in question followed by an establishment of the benefit-risk ratio. If the drug is judged to be safe and effective for the given indication, a marketing authorization (MA) is granted by the competent regulatory authority [1].

The conditions of the registration, typically the indication, patient population, posology and method of administration, warnings and contraindications are reflected in the label of a product (SmPC, PIL and label). The SmPC serves as a concrete guidance for physicians on how to prescribe and use a medicinal product. Deviations from the conditions of use set forth in the label are defined as off-label use [2]. Off-label prescribing is a common medical practice that is neither restricted to special clinical situations nor to single countries [3]. Although accepted in certain circumstances, the use of medicines for indications for which they have not been comprehensively assessed may expose patients to an unfavorable benefit-risk ratio. Consequently, there is a high need for regulation in this medical field. Drug uses outside the scope of the MA have to be identified, monitored and controlled in order to ensure patient safety.

In 2010, a serious drug scandal occurred in France involving a medicine that was also prescribed for off-label indications. The drug could be held responsible for hundreds of deaths. As a result, the French legislators implemented a new law aiming at strengthening the safety of medicines and health care products. Based on this reform, among others, France fundamentally changed the way how to regulate the off-label use of medicines. This new strategy will be presented and discussed in this thesis.

The paper starts with an overview about general aspects of off-label uses including definitions, frequencies, reasons for and benefits and risks of off-label prescriptions. Furthermore, the legal framework with focus on the EU will be presented. Off-label use constitutes a major challenge for health care professionals (HCPs), pharmaceutical companies and health insurances (the latter with regard to reimbursement). This will be specifically addressed in this thesis as well as off-label promotion and the informed consent process for patients treated with drugs outside the scope of the MA. Section 3 of this paper deals with regulatory aspects of off-label uses including variations of MAs and incentives provided by the EU for extensions of indications and for developments of drugs for children and orphan diseases. Section 3 describes France`s new framework for regulating the off-label use of drugs and in section 4 advantages and disadvantages of the new “off-label regulation” are presented taking into account other strategies for identifying, monitoring and controlling the off-label use of medicines. Presented facts and developments of off-label regulations are subsequently discussed and evaluated.

2. OFF-LABEL USE – GENERAL ASPECTS

2.1 Definition

The usage of an authorized medicinal product outside the terms of its MA is internationally described as off-label use [4]. However, there is no standardized definition existing in the relevant scientific literature and neither the German Medicine Act (AMG) nor the European regulations on human medicines (especially Directive 2001/83/EC) contain any common interpretation of the term.

The expression "off-label" per se derives from the US term "product labeling" which means all labels and other written, printed, or graphic matter upon any product or its containers [5]. The US "product labeling" is regarded as an equivalent to the European SmPC [6]. The SmPC reflects all parameters of a MA, typically including the indication, dosage, frequency and route of administration. Other important factors are the age range of patients, duration of treatment, and contraindications [2].

There is consensus that an existing MA is a mandatory prerequisite for off-label use but it is in particular unclear which parameters of the MA should be taken into consideration when classifying a drug prescription as off-label. It seems reasonable to question whether even slight modifications of the conditions specified in the product label are sufficient to consider it off-label use. This is particularly important with regard to reimbursement through national health insurance schemes and related recourse claims [7]. One further point is that a physician may not appropriately inform a patient about an off-label prescription simply based on the wrong assumption that a prescription does not fall under the scope of off-label use. This may lead to liability consequences for the physician and illustrates the importance of a clear legal definition of the term “off-label use” [7],[8].

The WHO states that all “deviations from the conditions of use set forth in the label constitute off-label use.” [2]. This is in compliance with the definition of the US Food and Drug Administration (FDA) which describes off-label use of a drug as follows: „Use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling.“ [4]. According to this „broad definition” which is also used by several other authors and/or institutions, all deviations from the parameters specified in the MA should be considered as off-label use [4],[7],[9],[10]. In annex I of the European Guideline on Good Pharmacovigilance Practices (GVP), the European Medicines Agency (EMA) specified that off-label use refers to “situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information” [11]. With the wording “intentionally used for a medical purpose” the EMA clearly distinguishes off-label use from other drug uses outside the MA such as medication errors (unintentional) and misuse (no medical purpose).

In the narrow sense, off-label use only comprises the use of a medicinal product outside the indications authorized by national or European regulatory authorities. Such a “narrow definition” is used by the Federal Joint Committee (G-BA) [12] and also article 35c(1) of Volume V of the Social Insurance Code (SGB V) restricts the usage of medicines outside the scope of their MA to unauthorized indica-

tions. However, the term “off-label” is not explicitly mentioned in this context. The narrow definition was taken as a basis for several legal proceedings dealing with off-label use [7].

Plate (2009) argues in her thesis that “use outside the terms of indication” does not adequately describes the term off-label use [13]. She identified seven categories of off-label use based on the parameters laid down in the SmPC. “Indication-based” off-label use means the use of a medicine to treat a different disease, entity, or stage. “Population-based” off-label use is seen when gender- or age-groups differ from those specified in the MA. “Dosage-based” off-label use is related to deviating treatment intervals, treatment durations or dosages. “Application-based” off-label use describes an irregular administration of a licensed drug (e.g. local versus systemic or intravitreal versus intravenous) and the term “contraindication-based” off-label use summarizes prescriptions against contraindications, warnings and interactions. A drug prescription that is not performed by a specialist although laid down in the SmPC is defined as “qualification-based” off-label use and “generic” off-label use is a result of cost-saving attempts. The latter may occur when the generic drug has less authorized indications than the reference medicinal product but is nevertheless delivered due to mandatory generic substitution [13]. To include all identified categories Plate defines the term off-label as use of an authorized medicinal product that is not described in the product labeling and in a way requiring a variation to the MA, extension of the MA or a new MA [13],[7]. Also other authors state that the variation rules can provide a useful element in assessing off-label prescriptions of a drug [14].

Off-label use should be distinguished from the use of an unauthorised medicinal product, that is, a product which does not have a valid MA in the European member state (MS) where it is being used. In this context, the G-BA clearly states that the “administration of pharmaceuticals not (yet) authorized in Germany is not included in the term off-label use" [12].

Off-label use takes place outside a clinical trial in the context of medical care - either on the basis of an individual treatment attempt or, if the treatment is already established," on the basis of standard medical care. The difference between experimentation and therapy lies mainly in the intent of the therapy. If the therapy promotes the best interest of the patient, the off-label usage is deemed therapy. However, if the purpose of the treatment is to gain general knowledge for a broader population then it is considered human experimentation and the rules laid down in Directive 2001/20/EC (“Clinical Trial Directive”) apply (corresponding to §§ 40 et seq. AMG) [15]

The aim of compassionate use programs is to allow patients with a chronic, seriously debilitating, or life-threatening disease who cannot attend a clinical trial early access to a treatment. The prerequisite for compassionate use is that no satisfactory authorized treatment exists and that the medicinal product concerned must either be the subject of a MA application or under evaluation in a clinical trial [16]. The guideline on compassionate use of medicinal products clearly differentiates compassionate use from off-label use of medicinal products by stating that “[…] compassionate use does not refer to the use of an authorised medicinal product for an indication different from the one mentioned in section 4.1 of the summary of product characteristics [..], i.e. off-label use” [17].

Off-label use could further be demarcated from the concept of "unlicensed" use which refers to the use of a medicinal product that has not been assessed or approved by the competent authorities including the use of an authorised medicinal product in a different pharmaceutical form (e.g. grinding a tablet into fine powder in order to administer it through a catheter with diluents added) [6],[18]. According to some authors, such a use should not be summarized under the term off-label due to the fact that a change in the pharmaceutical form may be associated with significant changes in the quality, efficacy or safety of the medicine and therefore requires a re-evaluation [7].

2.2 Frequencies of off-label use

The prevalence of off-label prescribing is difficult to estimate as reliable data are missing. On the one hand, this is based on the fact that prescriptions outside the terms of a MA are not registered separately by health insurances or other central locations. On the other hand, pharmaceutical companies are not obliged to provide accurate information on their product sales [19]. Nevertheless, studies published over the past ten years indicate that off-label use is widespread, both in the European Union (EU) and the United States (U.S.) [9]. High frequencies of off-label use are also reported in other countries [13].

Off-label use occurs in almost all medical areas. It is exceedingly common in paediatrics, oncology, neurology, infectology and geriatrics [9]. High rates of off-label prescriptions are also found in obstetrics and gynaecology [20].

The practice of prescribing medicinal products for conditions outside the scope of the label is found in approximately 50% of all physician prescribing in the U.S. [21]. According to Levêque (2008), findings of prospective studies undertaken between 1990 and 2002 showed proportions of off-label drug use in children and adults of 6.7-33.2% [22]. Gazarian et al. (2006) predicated that the extent of off-label use is reported to be between 7.5% and 40% in adults and may be up to 90% in some hospitalized children [23].

Radley et al. (2001) performed a study to systematically characterize the extent of off-label prescribing in general outpatient care. They found that 21% of all estimated uses for commonly prescribed medications were off-label. However, the magnitude of off-label prescribing varied widely, exceeding 50% for specific medications and drug classes. The greatest proportion of off-label use could be detected for gabapentin and amitriptyline hydrochloride, reaching 83% and 81%, respectively [24]. In Germany, the off-label use of medicinal products has been estimated to reach 20% of all prescriptions [25].

According to a survey performed by Conroy et al. (1999), 39% of drug prescriptions given to children in five different European countries were off-label [26]. The WIdO ("*Wissenschaftliches Institut der AOK*") indicates that up to 90% of all prescriptions for hospitalized children and adolescents are either off-label or unlicensed (i.e. without a formal MA). In case of outpatients, the rate is estimated to be >13% [27]. In general, the probability of receiving off-label prescriptions is higher in younger children and patients with special or rare conditions. Especially in neonatal care, almost all drugs (up to

90%) are used off-label [20]. It is postulated that off-label prescribing of drugs in the pediatric population is increasing rather than declining, partly based on an expanded use of psychotropic drugs [21].

In oncology, the rate of off-label use has been estimated to reach 50%, or even more [13],[28],[29]. Similar results have been reported in the U.S., where approximately half of the anticancer drugs are prescribed off-label [30]. Off-label drug use has been described for most cancer types [22].

On the basis of the available data, it can be concluded that the overall frequency of off-label use is high. Off-label prescribing seems to be an international, widespread and growing practice [21].

2.3 Reasons for off-label use prescription

The reasons for using a drug outside the specifications laid down in the label are diverse and complex. Before a medicinal product can be marketed, the pharmaceutical company must provide scientific evidence that the product is safe and effective by satisfying rigorous regulatory requirements. The MA is restricted to clearly defined conditions included in the label of the drug. However, in numerous instances, a medicinal product may also be used for other valuable medical purposes. This is especially true for drugs with a broad ranging mechanism of action (e.g. topoisomerase I inhibitors) [3]. Off-label use may originate from a presumed drug class effect (certain pharmacodynamics effect that is known to be present in other drugs of the same class), an extension to related conditions or an expansion to distinct conditions sharing a physiological link (e.g. the use of the antidiabetic drug metformin to treat polycystic ovarian syndrome) [31]. Furthermore, a physician may prescribe a drug to patients with less or more serious forms of the disease or to patients suffering from a disease that causes similar symptoms [32].

After market entry of a drug, a typical development pattern of off-label use can be observed: At the beginning, there are individual treatment attempts of some scientists or physicians which are reported in the scientific literature. These publications, small case series and congress reports are considered to be “evident” by other healthcare professionals and serve as "legitimation" for further and much more pronounced off-label uses. At the end, this process might even result in a situation where the off-label use is accepted as standard of good medical care [19].

As a general rule, newly approved drugs have very narrowly defined indications and may only be used in well-defined patient populations. This is based on the fact that pharmaceutical companies focus their clinical research on only some of the potential uses of a medicinal product as the process for obtaining a MA for an additional use is expensive, lengthy and unprofitable [18]. "It is generally burdensome to prove the risk-benefit ratio, and business concerns may prevail over other factors.” [18] It is postulated that the regulatory structure incentivizes pharmaceutical companies to seek a narrow indication in order to minimize the risk for delayed market entry and to reduce the investment in research [33]. Regulatory authorities also promote the emergence of narrow indications by pursuing the strategy of risk minimization. They precisely align the conditions of the drug approval with the inclusion and exclusion criteria specified in the phase III registration trials [4],[29]. As a consequence, a grow-

ing gap between the authorization status and the actual medical need in daily medical praxis can be observed (often in oncology) [29]. An increasing differentiation of diagnoses and treatment situations (e.g. breakdown of formerly uniformly classified tumor entities in different biological entities) further contributes to this situation. Usually, only the most common entities within the most common diseases constellations are included in the registration strategies for new medications [29].

It is also postulated that a lack of incentives (especially in case of off-patented drugs) prevents pharmaceutical companies from performing studies to support a MA extension. This is further enhanced by the fact that reimbursement for off-label uses is partly occurring [34]. A company that knows that an approved drug is used off-label could be reluctant in funding a clinical trial in order to obtain a MA extension as such trials are expensive. Furthermore, the study results could decrease sales by showing that the drug is ineffective or has significant safety problems [35]. An additional barrier is the issue of liability for adverse event associated with a drug use. The liability of a manufacturer is reduced if the use is not recommended in the label of the drug [34].

Off-label use is particularly intended to respond to unmet medical needs. For that reason it is often seen in pediatric, obstetric and geriatric practice and in patients suffering from cancer or rare diseases as these specific patient groups are excluded from many pre-marketing trials. On the one hand, they are outside the focus of industrial drug development due to limited market potential. On the other hand, pharmaceutical companies are reluctant (often based on liability fears) to enroll minors, pregnant women, and elderly people in clinical trials [32]. The recruitment of those subjects is generally more difficult (low number of patients, informed consent process more complicated, complex patterns of medication intake and comorbidities especially in older patients).

A further reason for off-label use of medicines is the scientific development and the slowness of the drug approval process. Medical practice and science are constantly evolving under everyday conditions. This dynamic medicinal progress is much faster than regulatory authorities can approve new drug uses [4],[18],[34].

Off-label use is partly due to illegal promotional activities of pharmaceutical companies [36] and in some cases it may be requested by patients pushed by the internet or other media for the non-authorised use of a medicine [18].

Off-label prescribing may also be based on inadequate physician´s knowledge of the current approved drug labels [30] or induced by governments for financial reasons [6],[37].

2.4 Benefits and risks of off-label use

In certain practice areas (such as oncology, neurology and paediatrics), off-label prescribing is extremely common and may be justified on several grounds [32]. Some medicines are prescribed off-label either to fulfill a public health need not covered by an existing MA or to ensure access to a medicine by certain patient subgroups [38]. It permits creative and flexible use of medications and promotes innovation in clinical practice, particularly when approved treatments have failed.(82) Further-

more, it offers patients earlier access to potentially valuable medications [31]. A prominent positive examples of off-label prescribing is aspirin which has been used off-label for lowering the risk of a second heart attack several years before efficacy could be demonstrated in clinical trials [39]. Other examples are beta-blocker [40] and misoprostol [35]. It was concluded that "as long as drugs are safe, well tolerated, and relatively inexpensive, off-label use generates little concern" [40].

Despite several benefits of off-label use, the lack of regulation in this area may create some important risks [41]. First and foremost, off-label prescriptions are not subject to the stringent drug approval process laid down in various national and European regulations and guidelines. A MA applies exclusively to the parameters reviewed and accepted by regulatory authorities and is based on a positive benefit-risk ratio evidenced by expensive and time-consuming clinical trials. Rigorous drug licensing and monitoring procedures were introduced as a reaction to serious drug scandals having occurred in the past. It became evident that an uncontrolled access to drugs produces a risk for the population [3].

If a medicine is used outside the scope specified in the MA and described in the corresponding label (SmPC), there is no guarantee that it is safe and effective [43]. Many factors could be different in the off-label compared to the on-label setting including the age of the patient, range of co-morbidities, use of concomitant medication, drug-disease interactions and differences in pharmacokinetics (PK) and pharmacodynamics (PD). These differences may influence the effectiveness or safety of a medicine [42]. This especially applies to special patient populations such as children or elderly people. While many drugs have the same effect and a similar safety profile in adults and children, this is not always the case. Typical examples are tetracyclines causing mottling of teeth in children or selective serotonin re-uptake inhibitors (SSRIs) leading to suicidal thoughts in adolescents [21]. Due to varying PK and PD activities it is not appropriate to simply extrapolate from adult data when prescribing a drug to children that is only approved for adults as this may lead to wrong dosages [23].

Off-label use lacks rigorous and thorough scientific scrutiny and may pose enormous unknown risks to the health and safety of the public [29],[44]. Some long established off-label prescriptions have been shown to either be ineffective or harmful when subjected to proper evaluation [23]. However, there is no consistent evidence on whether adverse drug reactions occur more often during non-licensed drug use (including off-label use). In some studies, no significant differences between on-label and off-label prescriptions could be detected [13],[19]. Nevertheless, the G-BA stated that the risk of off-label use could be demonstrated by severe and sometimes even fatal side effects provably related to prescriptions outside the terms of the MA [45]. This statement is supported by investigations performed by the multi-disciplinary working group RADAR (Research on Adverse Drug events And Reports). Based on systematic evaluations in the context of post-marketing surveillance programs it was concluded by this group that serious and unknown ADRs are frequently associated with off-label uses for which no scientific evidence exist [10]. According to a study report published by the EMA, off-label use of medicines in children may lead to increased incidence and seriousness of adverse drug reactions [46]. The potential for harm seems to be greatest when the off-label use lacks a solid evidentiary basis [32]. This

is of particular relevance as a survey of 150 million off-label prescriptions in the US indicated that 73% had little or no scientific support [24]. The fact that a substantial number of drugs is often prescribed in the absence of good evidence could also be demonstrated by another study [47]. It is postulated that many physicians fail to demand solid evidence for their prescribing choices. They cannot weighing up the safety and efficacy data in the same way as a licensing authority and rather rely on experiences, anecdotal reports and key opinion leaders to guide their treatment decisions [32],[48].

One further critical point is that most patients do often not know when a drug is being prescribed for a condition for which it has not been approved [49]. Such a missing informed consent may moreover lead to increased liability of the physician [50]. In case of unexpected events associated with off-label use, there is a high risk that neither the company nor the health authorities take any legal or ethical responsibility [3].

General underreporting of patient damages by physicians and the tendency of pharmaceutical companies to deprive the public from negative information on off-label uses of their drugs [25] combined with the fact that in the past health authorities did not routinely monitor, collect, or evaluate information regarding off-label drug use constitute a further risk for the patient [10]. Accordingly, SmPCs are not adequately updated and physicians have no access to critical information on how to correctly prescribe the drug in an off-label setting [34]. It is even possible that physicians are not informed in time of any drug shortage by the manufacturer as it happened with Prostin, a drug used off-label as an emergency treatment for infants to maintain the patency of the ductus arteriosus [51].

A further concern is that off-label use of drugs may undermine the incentives for manufacturers to perform rigorous studies for extending a MA. Off-label use may even "encourages them to game the system by seeking approval for secondary indications for which clinical trials are less complicated and less expensive" [31]. A drug company may simply rely on the physician community to discover and spread information with regard to off-label use [41].

Finally, in an era of rising healthcare costs, it is worth mentioning that off-label use can make a negative contribution, especially in case of newer, more expensive drugs [31]. A typical example is Gabapentin, a very expensive drug which is prescribed for approximately fifty off-label uses including bipolar disorder without having reliable data on effectiveness [15].

In conclusion, off-label prescribing is a potentially risky clinical practice which should only be used in cases where there is no licensed product available that meets the medical need of the patient.

3. LEGAL FRAMEWORK

There are great national differences in the practice and regulation of off-label use [48]. In Europe, off-label prescribing by physicians is generally allowed. However, individual MS have their own rules with regard to off-label prescribing and reimbursement [52]. In several EU countries, the practice is regulated by law, whereas in others, it is covered by good practice regulations including treatment

guidelines, general professional recommendations and reimbursement decisions [48],[37]. Some authors criticize the lack of effective legislation in the EU and claim that the different regulations provided at national levels are unclear [28]. A recent survey performed by the Pharmaceutical Committee of the European Commission in October 2012 substantiates the statement that there are no harmonized rules within the EU. All MSs were requested to provide information concerning the following question: "*In your Member State, what is the approach to off-label use and what are its main characteristics? Please also specify if there is none.*" [53]. The Commission summarized the replies and explained that there are currently different steps and ways to approach the off-label use issue in the EU [54]. To improve the situation, some authors call for harmonization of the regulations, for example through creation of lists/compendia of acceptable off-label prescriptions by the EMA [28].

3.1 European legislation

Despite its common practice, the European legislation does not directly regulate the off-label use of medicinal products [9]. Regulatory health authorities are only empowered to regulate the licensing process and the content of the label but not the way the products are ultimately used in medical practice [37]. No general guidelines exist defining what constitutes the "correct off-label use of medicines"[18]. There is even no common legal definition of the term "off-label" (see chapter 2.1).

According to article 6 of Directive 2001/83/EC, medicinal products have to obtain a MA from the relevant EU competent authority before being placed on the European market. A MA is granted if the benefit-risk ratio of the medicinal product in the intended use is considered to be favorable. The decision made by the competent authority follows a comprehensive and independent assessment of all available quality, safety and efficacy data submitted by the manufacturer.

The EU law provides very limited exceptions from this general rule. Accordingly, no MA is required for [55],[18],[37],[56]:

- medicinal products in authorised clinical trials (art. 3(3) of Dir. 2001/83/EC)
- magistral and officinal formulas (art. 3(1) and (2) of Dir. 2001/83/EC)
- medicinal products when one of the specific exceptions listed in either Dir. 2001/83 or Regulation 726/2004 applies (e.g. emergency situation (art. 5(2) and (3) of Dir. 2001/83/EC); compassionate use, where there is no other treatment available (art. 83 of Reg. 726/2004); or "special need exemption" according to art. 5(1) of Dir. 2001/83/EC).

  The latter condition is intended to fulfill special needs of an individual patient under the direct personal responsibility of the prescribing physician. In such a situation, a MS may allow the supply of medicines for unauthorised uses [1].

In general, exemptions from the MA requirement should be interpreted restrictively [37]. With regard to off-label use it is stated that "[s]imilar to the situation of prescription of an unauthorised medicinal product, EU pharmaceutical law does not preclude the prescription of an authorised product for an unauthorised indication ("off-label" prescription) at the discretion of the doctor and at his own responsi-

bility." [56]. According to a statement given by the European Commission in the Sanofi-Aventis/Zentiva merger decision, the off-label use "simply implements the generally accepted principle of therapeutic freedom for prescribing physicians" [55]. However, the EU law does not provide any authorization for broader off-label use. This is evidenced by the provisions inserted in article 5(2) of Directive 2001/83/EC binding the existing exemptions from the MA requirement to specific derogations in case of major public health threats (off-label use is not mentioned in this context) [55]. Furthermore, the exceptional nature of off-label use can be demonstrated by the fact that it is not accepted as a satisfactory method of treatment for the application of article 3(1)(b) of Regulation (EC) No 141/2000 (see related Commission Communication (OJ [2003] C 178/2) [55].

In conclusion, off-label prescribing can only be an option in exceptional circumstances where no other authorized drug is available to treat the special condition of an individual patient. The observed trend towards encouraging off-label use by official bodies for financial reasons is considered to be incompatible with the EU regulatory framework [37],[55],[56].

3.2 The perspective of health care professionals

In general, physicians enjoy freedom to prescribe, meaning that they are allowed to administer or prescribe a marketed medicinal product to their patients for any indication (approved or unapproved) [18]. However, a high degree of caution must be exercised by a physician when prescribing off-label. Physicians are professionally accountable for their treatment decisions and in case of off-label prescribing, their responsibilities are even enhanced (see article 5(1) of Dir. 2001/83/EC) [6]. They are obliged to respect their professional duties and responsibilities under national law as well as relevant ethical aspects [18]. In particular, they have to take into account the accepted standard of good medical care. If an off-label prescribing does not comply with this medical standard, it can lead to malpractice liability [32]. The medical standard of care is determined by the medical profession and can outpace the authorities' MA approval [57]. This is especially true when medical practice and science are evolving faster than regulatory authorities can act [18].

Situations of appropriate off-label prescribing can be summarized as follows:

- Compelling clinical reason, i.e. no authorized alternative treatment available or specific patient characteristics (e.g. age, intolerance) that do not allow the use of an authorized medicine [32],[48].
- Solid scientific basis (requirement weakened if no suitable treatment available): Physicians have to evaluate if there is sufficient scientific evidence and/or medical experience to justify their actions [32],[6]. They have to consider professional standards, medical treatment guidances and relevant available literature and carefully balance the risks and benefits before prescribing a drug outside the terms of the MA [18]. Physicians have to be fully informed about the characteristics of the drug and should communicate with other medical experts, if necessary [48].
- High degree of respect for patient rights: A physician is obliged to act in the patients' best interest whilst preserving his autonomy (informed consent requirement, see section 3.2.1) [18].

- Clear and accurate documentation: This includes reasons for off-label prescribing and following-up measures [18]. In addition, healthcare professionals and patients play a crucial role in monitoring the safety of medicinal products and/or reporting of adverse drug reactions (recital 21 of Dir. 2010/84/EC). Therefore, physicians are responsible for reporting suspected adverse reactions related to off-label use to pharmaceutical companies and/or competent authorities [6]. However, physicians usually have little incentive to report adverse drug reactions. This is partly for reasons of liability (physicians are hesitant to report possible mistakes to competent health authorities) [18]. Directive 2010/84/EC tries to address this issue by facilitating the reporting of suspected adverse reactions and by making methods for such reporting easily accessible for both, healthcare professionals and patients (recital 21 and art. 102). "However, it remains to be seen whether the reform will actually encourage doctors to report adverse drug reactions attributable to off-label uses […]." [18].

Overall, off-label prescribing is extremely challenging for physicians. On the one hand, they are interested in providing the best treatment options for their patients and are therefore in support of off-label use [15]. Especially in situations where no authorized treatments are available, physicians are ethically obliged to search for alternatives. They may even be obliged to prescribe off-label in order to avoid liability under the civil law [58]. On the other hand, physicians have to take into account that the safety and efficacy of the application have not been fully established. However, in daily practice it is often difficult to decide if the intended prescription is sufficiently supported by scientific evidence [8].

One further important point is that the physician's responsibilities are overall enhanced when prescribing a drug for off-label use (burden of proof is shifted to the physician) [18]. "If the physician fails in these enhanced responsibilities and the off-label use causes injury to the patient, the physician is not only exposed to civil liability claims for fault/negligence, but possibly also to criminal and disciplinary sanctions."[6].

With regard to liability, physicians are advised to check if the off-label treatment is included in the insurance cover (depending on individual agreement between the physician and his liability insurance). Usually, all treatments are covered that are generally accepted by medical science. This includes off-label applications that are already established as standard of medical care. All other treatments that might be associated with special risks should be insured separately by the physician [58].

3.2.1 Informed consent

The patient´s informed consent is considered to be an important factor although not explicitly required by the EU pharmaceutical rules [18]. It is generally recognized that "[p]atients have a fundamental right to be informed about the treatments they receive and to be put in a position to actively participate in the treatment decisions." [14]. The free and informed consent of the patient must be respected by all stakeholders and EU Member States are also bound to protect these rules [14].

The informed consent requirement especially applies to off-label prescribing when strong scientific support is missing. Prior to any off-label treatment, physicians have to comprehensively inform the patient about the drug, including that the proposed use is outside the specifications laid down in the SmPC. In addition, the prescriber has to explain the reasons for the off-label use, its pros and cons and available alternatives. The patient should be aware of the fact that off-label use may be associated with higher and partly unforeseeable risks [18]. Furthermore, he/she has to be informed about the fact that insurers may refuse to cover the costs for the off-label application which may lead to a high financial burden for the patient [9]. At the end of the process, the patient must explicitly provide written consent to the off-label treatment. Case law across Europe indicates that failure to obtain such an informed consent constitute a violation of the duty of medical care [14]. Patients who are not being adequately informed by their physicians are entitled to bring damages claims [9].

3.3 Reimbursement

Article 4(3) of 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." Accordingly, there is no mandate for regulating the reimbursement of medicines on EU level. Whether or not the costs for off-label use are covered depends on the health system established in each MS. There are specific insurance coverage policies and in some countries, there are even differences between off-label applications in community settings and hospitals [22],[18]. State programmes and insurances often deny reimbursement of costs arising through off-label prescriptions [3]. As an example, an overview of the reimbursement situation in Germany will be given.

3.3.1 Reimbursement of off-label use in Germany

In Germany, the off-label use of medicinal products is either regulated by the Medicines Law or the Social Law [20]. As in other European countries, physicians are permitted to prescribe medicinal products on an off-label basis within their therapeutic flexibility [9]. However, pharmaceuticals can only be prescribed at the expense of the statutory health insurance if they are used for the treatment of a disease for which the pharmaceutical company has obtained a MA from the relevant authority [12]. This requirement is aimed at ensuring drug safety in the interest of patients. Furthermore, it should avoid that drug companies bypass the complex drug approval process through widespread off-label use. Nevertheless, the German case law clearly points out that patients should have the right to receive off-label drugs, provided that some specific conditions are met.

Before issuing a panel prescription (German "*Kassenrezept*"), a physician has to check if the indication is included in the „positive list" of the Pharmaceutical Directive which is published by the G-BA. According to § 35c(1) of the SGB V, the Federal Ministry of Health is empowered to appoint and commission expert panels at the Federal Institute for Drugs and Medical Devices (BfArM) "to deter-

mine in which cases authorized pharmaceuticals can be used to treat diseases, even though the pharmaceutical has not been authorized for the disease in question […].” [12].

Based on this provision, the BfArM has established four “off-label expert panels” covering the following medical areas: oncology, neurology/psychiatry, ophthalmology and infectious diseases with emphasis on HIV/AIDS [59]. These expert panels are delegated by the G-BA to assess the current status of scientific knowledge regarding the off-label use of pharmaceuticals [12]. Their recommendations are forwarded to the G-BA. The G-BA is then responsible for defining which of these assessed pharmaceuticals are “prescribable for unauthorized indications” and therefore suitable to be included in part A of appendix VI of the Pharmaceutical Directive [12]. Listed indications can be refunded by health insurance companies, provided that the MAH has given informed consent (§ 35c(1) SGB V). Off-label uses which are considered as “non-prescribable” are included in part B of appendix VI. Currently, each list (part A and B) include eleven off-label indications.

If a physician intends to prescribe a drug for an off-label indication that is not listed in appendix VI of the Pharmaceutical Directive, the costs can only be refunded if the following three key requirements are fulfilled [58],[20]:

- serious disease (life-threatening or significantly affecting the quality of life),
- no alternative treatment available and
- reasonably chance for treatment success (research results are available indicating that the medicinal product could be authorized for the relevant indication).

The latter condition applies if

a) the manufacturer has already applied for a MA/MA extension (i.e. results of a controlled clinical trial phase III show clinically relevant effects and clinically relevant benefits with acceptable risks, respectively) or

b) outside the MA procedure, if publications are available that allow reliable and scientifically verifiable statements with regard to treatment success and if consensus exists among scientific experts.

These above mentioned key requirements were determined in a BSG (federal social court) ruling from March 19, 2002 (B1 KR 37/00 R, so-called “Sandogobulin decision”).

In a judgement of the BVerfG (federal constitutional court) dated December 6, 2005 (1 BvR 347/98, so-called „Nikolaus-Beschluss“), it was decided to widen the conditions based on the fact that the previous requirements are not in compliance with the fundamental rights stipulated in the German Basic Law. Accordingly, the costs for off-label use should also be refunded if there are only weak references for efficacy, provided that the patient suffers from a life-threatening condition and alternatives are missing [20]. Based on a further judgment of the BSG in October 2004 (B 1 KR 27/02 R, so-called „Visudyne decision“), the statutory health insurance should also be obliged to bear the costs for off-label prescription in rare diseases, as far as systematic research is not feasible due to the rarity of the condition (“emergency-like situation”) [58].

Starting from the decision of the BVerfG in 2005, the BSG further specified and liberalized the requirements in a decision from April 4, 2006 (B 1 KR 7/05 R). A physician has now the possibility "not to decide by himself for off-label drug prescription, but to get a vote of credit from the accordant health insurance company" [20]. In case of a decline he is advised to expose a private prescription [20]. If a physician does not comply with these provisions, he may be called to reimburse personally for the off-label prescription. In this context, it should be mentioned that, in Germany, the reimbursement issue is mainly restricted to statutory health insurances as private health insurances normally pay for off-label uses [58]. This situation may lead to an unequal treatment of patients [60].

3.4 The perspective of the pharmaceutical company

On the basis of a recent reform of the EU pharmacovigilance framework more attention was given to the off-label use of medicinal products [37]. The so-called EU "Pharma Package" was, inter alia, intended "to strengthen the European Union's legal framework by establishing mechanisms to improve data collection, processing and dissemination, including in the case of off-label use." [18].

In general, it is the MAH's responsibility to continuously monitor the quality, safety and efficacy of its medicinal products. Any changes that might have an impact on the MA have to be reported to the competent authorities and the product information has to be kept up to date (recital 12 of Directive 2010/84/EC). Due to the limited data of a medicinal product at time of approval, post-marketing findings may have clear safety implications. This is also true for the outcomes of off-label uses. Therefore, it is particularly required to systematically evaluate and report effectiveness and safety of a medicinal product with regard to non-licensed usages [61].

Prior to the implementation of the "Pharma Package", the MAH was not obliged to report adverse drug reactions associated with off-label uses to the agencies. This was simply based on the fact that the previous definition of the term "adverse reaction" did not cover usages of a drug outside the specifications of a MA. According to article 1(11) of Directive 2001/83/EC, the term was defined as "[a] response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease […]."

Directive 2010/84/EC clearly highlights the fact that medicinal products are also used off-label and that the MAH's responsibilities should therefore be expanded to any usages outside the terms of the MA (recital 12 of Dir. 2010/84/EC). Consequently, the definition of the term "adverse reaction" was amended in order to cover "noxious and unintended effects resulting not only from the authorized use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorization" (recital 5 of Dir. 2010/84/EC).

Furthermore, the MA holder is now required to bring to the attention of the health authorities any new information which might influence the evaluation of the benefits and risks of the medicinal product, including data on the use of the medicinal product where such use is outside the terms of the MA (art. 23(2) Dir. 2001/83/EC amended by Dir. 2010/84/EC).

Directive 2010/84/EC also replaced the definition of post-authorization safety studies (PASS) in order to expand it to usages outside the terms of the MA. Accordingly, health authorities are now able to require pharmaceutical companies to perform PASS for off-label uses. However, this broad scope is not applicable to post-authorization efficacy studies [37].

One further change refers to the grounds for a suspension, revocation, withdrawal or variation of a MA (art.116 of Dir. 2001/83/EC). In the previous definition, this was only possible in cases "where that product proves to be harmful in the normal conditions of use". The new wording also includes unfavorable risk-benefit balances of a medicinal product when used outside the terms of the MA [37].

According to module VI of the Guideline on Good Pharmacovigilance Practice (GVP), the requirements stipulated for the collection, management and reporting of events or patterns of use are not applicable for off-label use. Only reports of off-label use associated with suspected adverse reactions have to be reported as individual case safety reports (ICSRs) to the competent authorities [62]. Furthermore, off-label uses constituting safety issues that may lead to a change in the risk-benefit balance of the pharmaceutical product have to be notified. All other reports have to be collected and presented in periodic safety update reports (PSURs) to the competent authorities [63].

The MA holder has an obligation to review the worldwide literature in order to obtain data on experiences with the medicinal product. This also applies to off-label uses. All relevant data have to be evaluated and included in the PSUR [62]. If the MAH becomes aware of a pattern of use of the medicinal product outside the terms of the MA, such information has to be commented taking into account clinical guidelines, clinical trial evidence and availability of alternative treatments [63]. The MA holder is also required to discuss the likelihood of off-label use of a medicinal product when drafting a risk management plan [64].

With regard to liability of pharmaceutical companies, the regulatory framework on pharmaceuticals and the European Product Liability Directive apply simultaneously [6]. In general, MA holders can be held liable for any harm caused by defective medicines they produce, provided that the medicine is prescribed within the terms of the MA [65]. According to §84 of the German AMG, a MA holder is obliged to compensate for damages resulting from the administration of a medicinal product when the use is in accordance with its intended purpose or when the damage has occurred as a result of labeling, expert information or instructions for use which do not comply with current medical knowledge. In this context, the term "use in accordance with its intended purpose" is not only restricted to the conditions specified in the MA but may also include off-label prescriptions that are publicly known, account for a considerable percentage of sales, are directly or indirectly promoted by the pharmaceutical company and/or are reasonably foreseeable [6],[8],[18].

From a product liability perspective, MA holders are well advised to mention any risks associated with the use of a medicine in the product information. This also includes side effects related to off-label use. MA holders can be held liable if they fail to provide this information [6],[18].

However, a MA holder may be able to escape liability if not being aware of the off-label use (physicians have no legal obligation to inform a manufacturer about an off-label prescribing). Another scenario could be that an authority refuses to include a warning (or contra-indication) on risks associated with off-label uses in the SmPC although applied for by a MA holder. This might be simply due to the fact that the authority would like to avoid indirect off-label promotion through insertion of such a warning in the product information [6].

According to some authors, "generic" off-label use may raise specific concerns, especially with regard to liability. However, it is considered that generic companies can be held liable in case of adverse events associated with an off-label use as long as the off-label indication is not explicitly mentioned as a contraindication in the label [7].

3.5 Off-label promotion

Advertising of medicinal products includes "any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products" (art. 86 of Dir. 2001/83/EC). According to article 87(2) of the Community Directive, all parts of the advertising must be in compliance with the particulars listed in the SmPC of the respective medicinal product. Advertising shall encourage the rational use of the medicinal product and shall not provide misleading information (article 87(3)). Promotion of off-label use is generally banned in the EU. In this context, article 87(1) of Directive 2001/83/EC stipulates that MSs are obliged to prohibit any advertising of a medicinal product in respect of which a MA has not been granted in accordance with Community law. According to a judgment of the Court of Justice of the European Union (CJEU), these rules do not only apply to the pharmaceutical company marketing the drug but also to third parties acting outside any commercial or industrial activity [37]. The requirements stipulated in the Community Directive are reinforced by self-regulation mechanisms established by international trade associations. They engage member pharmaceutical companies to restrict promotion of non-approved drug uses [36]. Directive 2001/83/EC explicitly recognizes the voluntary control of advertising of medicinal products by self-regulating bodies in addition to judicial or administrative proceedings (article 97(5)). Accordingly, the European Federation of Pharmaceutical Industries and Associations (EFPIA) established a "Code of Practice on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals". This Code reflects the requirements of Council Directive 2001/83/EC and provides a more detailed framework that can be used as a reference document by all Member State private associations [66].

Despite the fact that advertising of medicinal products is extensively regulated in the EU, illegal off-label promotion practices are commonly observed (e.g. in the UK) [36]. This is of relevance as it is reported that a high percentage of the physicians (in Germany) receive their information from the industry [20]. Pharmaceutical companies who are found to have illegally promoted off-label drug use may face serious consequences in the EU [9]. Member States are required to implement adequate and effective methods to monitor the advertising of medicinal products including legal provisions (art. 97(1) of

Dir. 2001/83/EC). In Germany for example, administrative fines of up to €50,000 per incident may be imposed by healthcare supervisory authorities. However, such administrative actions have yet been applied very rarely [9]. In addition, the consequent risks for manufacturers seem to be comparatively low. Nevertheless, there have been extensive litigations between pharmaceutical companies and their competitors, consumers or fair trade protection organizations [9].

In contrast to the situation in the EU, off-label promotion is vigorously prosecuted in the United States and recently implemented measures are intended to encourage physicians to recognize and report suspected untruthful or misleading drug promotion. Over the last ten years, pharmaceutical companies had to pay fines and fees to settle criminal and civil cases of tens or hundreds of millions of dollars.(9)

4. REGULATORY ASPECTS WITH REGARD TO OFF-LABEL USE

The widespread off-label use may pose enormous unknown risks to the public health, especially due to the lack of regulation in this area. An optimal way for solving this problem would be to study the off-label condition (e.g. new indication) in well-defined clinical trials. Effective and safe uses could then be officially approved by health authorities [34]. In theory, there is a high need for extensions of MAs [38]. However, a corresponding application can only be applied for by the pharmaceutical company holding the MA of the respective drug [45].

The financial and procedural effort as well as the time needed for obtaining an extension of a MA depends on the kind of change that has to be evaluated by the regulatory authority. With regard to the "broad" definition all deviations from the conditions of use set forth in the SmPC constitute off-label use (see section 2.1). This definition includes the addition of new indications but also applies to other amendments of the SmPC such as changes of the target population, posology and method of administration, or changes of warnings and contraindications. Thus, off-label use may range from marginal deviations from the prescribing information to significant changes, including reformulations of the drug [14].

The scope of what can be considered a variation to the terms of a MA is defined in Commission Regulation (EC) No 1234/2008. According to article 1 read in conjunction with annex I of this "Variation Regulation", changes to the strength, pharmaceutical form and route of administration require the application of a MA extension. Such changes are considered to be so significant that the legislation demands approval through a separate MA procedure.

However, variations related to the addition of a new therapeutic indication or to the modification of 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 (annex II

of Reg. (EC) No 1234/2008). Therefore, in most cases it is sufficient to submit a type II variation for getting an off-label use approved.[1]

The procedural effort for such a type II variation is relatively low and strictly regulated. However, the clinical development process required for demonstrating efficacy and safety of an already approved drug against a new medical condition (e.g. indication) is long, expensive and laborious and may be accompanied by recruitment problems in case of orphans/paediatrics or problems with the informed consent in special patient groups [4],[68]. Consequently, those clinical trials will most likely not be undertaken if the product has not been particularly profitable or successful and an expansion of the MA is supposed to be financially unsustainable. This is also true if the patent period of the drug is nearing its end or if the patent has already been expired primarily because of generic competition [21]. Generic drug companies are generally not interested in sponsoring a costly clinical trial and in case of "[…] brand-name drugs that are already widely used off-label, conducting costly clinical trials that could produce non-supportive evidence is a potentially risky business decision." [31]. Finally, due to the fact that off-label use is both allowed and common in medical practice, the MA holder may not have a financial incentive to authorise new indications.(63)

The European legislators have created incentives in order to encourage the further development of already authorized medicinal products. According to article 14(11) of Reg. (EC) No 726/2004 and article 10(1) fourth subparagraph of Directive 2001/83/EC as amended by Directive 2004/27/EC, an extra one-year market protection can be obtained if a new therapeutic indication is registered within 8 years after the first MA (so-called "8+2(+1) exclusivity formula"). Such an extra market protection can only be applied for once. It is granted if the new indication brings significant clinical benefit over existing therapies. Detailed specifications are given in the corresponding EC guidance [69]. According to data published by the EMA, 1.92 extensions of indications per product are granted by the EMA (average value of the years 2004 to 2011). Only eight extensions of market exclusivity were approved between 2008 and 2012. In six cases, the application was rejected [70].

In case of well-established substances, a non-cumulative period of one year of data exclusivity can be granted if an application is made for a new indication, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication (art. 10(5) of Dir. 2001/83/EC).

[1] Commission Regulation 1234/2008 has been recently updated by Regulation (EC) 712/2012. One of the main changes introduced by this new Regulation concerns the expansion of the rules laid down in the "Variation Regulation" to purely nationally approved medicinal products. The amended "Variation Regulation" came into force on 4th August 2013. Before this date, variations of purely national authorizations were processed on a national level with partly different rules (according to national law). In Germany for example, changes of information included in the SmPC such as therapeutic indications generally required approval by the BfArM (§ 29(2a)) - a process comparable to a type II variation. However, addition or modification of an approved indication which is to be classified into another therapeutic area required an application for a new MA (§ 29 (3) AMG). In the past, such a national approval process was generally long-lasting (partly two or more years) [4]. Therefore, it can be assumed that this national requirement has not contributed to an improvement of the off-label situation in Germany.

Overall, the incentives afforded by these provisions are insufficient in persuading a commercially driven pharmaceutical company to seek an extension of a MA. Furthermore, incentives may possibly become effectless when indications are not taken into consideration in the search for cost-effective alternative medicinal products. This means that substitution by discounted generic drugs is partly based on the active ingredient, irrespective of whether or not the indication for which the drug is prescribed for is included in the SmPC ("generic off-label use") [13].

In addition to the incentives mentioned above, the EU implemented new regulatory instruments which will most likely contribute to a reduction of off-label use in the future [4]. These include, on the one hand, Regulation (EC) No 141/2000 on orphan medicinal products and, on the other hand, Regulation (EC) No 1901/2006 on medicinal products for paediatric use.

The purpose of the "Orphan Drug Regulation" is to encourage access to medicines for rare diseases (affecting not more than five in 10 thousand persons in the Community) by providing incentives for the research, development and placing on the market of designated orphan medicinal products. Sponsors of designated orphan medicines are eligible to benefit from the following incentives [71],[72]:

- Assistance with development of the medicine
- Reduced fees for pre-authorization and post-authorization activities (such as protocol assistance, MA application, inspections, variations etc.)
- Supporting research by providing funds
- Protecting from market competition once the medicine is authorized by offering a market exclusivity of ten 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.

Ten years after implementation of the "Orphan Drug Regulation", 62 orphan designated medicines had been authorized for marketing in the EU covering a wide variety of rare diseases such as many genetic diseases and rare cancers. It is estimated that more than 2.6 million European patients have benefited from this development including children and newborn babies. It is further suspected that more orphan medicines will be coming to the market in the coming years [73]. The EMA concluded that the orphan legislation in Europe has been a success so far [74]. The increasing number of authorized medicines for patients suffering from rare diseases may also contribute to a reduction of off-label use in this area.

Many of the medicinal products used to treat the paediatric population have not been studied or authorized for such use and may therefore lead to increased risks of adverse reactions in children, ineffective treatment through under-dosage, non-availability of therapeutic advances, suitable formulations and routes of administration, as well as use of magistral or officinal formulations which may be of poor quality. To address this problem, Regulation (EC) No 1901/2006 provides 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 [75].

If the drug development is compliant with an agreed paediatric investigation plan (PIP) and the results of the studies are included in the SmPC of the relevant drug, the applicant is rewarded with a 6-month extension of the supplementary protection certificate (SPC). In respect of orphan medicinal products, the reward consists of an extra two years of market exclusivity added to the existing ten years awarded under the "Orphan Drug Regulation". In order to establish incentives for authorized products no longer covered by intellectual property rights, a new type of MA, the Paediatric Use Marketing Authorization (PUMA) was established. PUMA applies specifically to medicinal products developed exclusively for use in the paediatric population and is rewarded with an 8 years of data and 10 years of market exclusivity [75],[76].

In a recent report on experiences with the "Paediatric regulation" published by the EMA it is stated that paediatric development has become an integral part of the overall development of a product. More medicines are now available for children and the framework put in place by this Regulation is considered to be a major step forwards in terms of public health protection for the paediatric population. However, up to now only one PUMA has been granted. It was pointed out that "[c]ompanies seem to fear that market exclusivity will not prevent physicians from continuing to use competitor products with the same active ingredient off-label, at lower costs, or that substitution for cheaper adult forms takes place at the level of pharmacies."[75].

There is also a theoretical concern that companies are reluctant to develop new indications, pharmaceutical forms and new routes of administration to avoid being bound by the obligation under article 8 of the "Paediatric Regulation", i.e. performing studies in the paediatric population in accordance with an agreed PIP. This could lead to a deterioration of the off-label situation in the EU. However, the EMA states that there is no evidence of such an effect [75].

In conclusion, one of its explicit goals – the reduction of the off-label use of drugs in the paediatric population – cannot completely be solved by the "Paediatric Regulation". Especially, the off-label use of "well-established" products will remain an issue.

5. FRANCE´S NEW FRAMEWORK FOR REGULATING OFF-LABEL USE

As an example of a recent approach to regulation of off-label use the French new legislation is discussed further.

5.1 France's new regulatory framework

A recent drug safety scandal involving Mediator® (benfluorex), a medicine approved for the treatment of diabetes but also used off-label as an appetite suppressant, paved the way for major changes in the French regulatory framework. Mediator® was withdrawn from the French market in November 2009 following evidence that it caused serious and sometimes fatal valvular heart diseases (the drug was associated with as many as 2,000 unnecessary deaths) [77],[78].

The so-called "in-depth" reform of the French regulatory system resulted in law number 2011-2012 of December 29, 2011 aiming at strengthening the safety of medicines and health care products [79]. The law consists of a long list of articles modifying numerous articles of the French Public Health Code (CSP) and some articles of the French Social Security Code (CSS) [77].
In principal, the Act which also transposes the European Pharmacovigilance Directive 2010/84/EU on the Community Code into French law focuses on four key aspects [80]:

- Increasing the transparency by strengthening the rules governing disclosure of conflicts of interest
- Replacement of the French Agency for the Safety of Health Products (Afssaps) by a new healthcare product regulatory body, called ANSM (National Agency for the Safety of Medicinal and Healthcare Products) which is provided with greater power and responsibilities
- Impacting regulations of the lifecycle of a medicinal product with regard to marketing authorization, reimbursement, advertising, promotion, distribution, prescription, dispensing and vigilance and
- Changing the regulations for medical devices.

The recently amended law also fundamentally changed the way how to regulate and monitor off-label use of otherwise licensed medicines in France. Off-label prescription, also reported as a widespread practice in France, was previously not subject to rigorous legal restrictions [78],[81].

According to article R. 4127-8 of the CSP, physicians are free to prescribe medicines that they consider to be the most appropriate in the given situation, provided that the prescription is within the limits established by law. Physicians have to restrict their prescriptions to what is necessary with regard to quality, safety and efficacy of patient care without neglecting their moral duties. Furthermore, they have to balance the advantages, disadvantages and consequences of the contemplated treatment against other existing therapies [38]. Based on this provision, HCPs are principally allowed to prescribe drugs outside the terms of the MA. However, article 18 of the reform introduced a new article L5121-12-1 into the French Code of Public Health that specifically restricts off-label prescriptions of medicinal products to cases where no other appropriate alternative drug with a MA or a cohort "temporary authorisation for use" (ATU) to this prescription exist in France. In addition, one of the following conditions must apply [77],[43],[38]:

- a "temporary recommendation for use" (RTU) is granted by the ANSM for the contemplated indication or condition of use **or**
- the prescriber considers it essential, given the data acquired in science, to improve or stabilize the clinical condition of the patient.

By this rule, the French legislator highlights that some off-label prescriptions are considered necessary to fulfill a public health need not covered within the scope of an existing MA. However, the new law clearly indicates that off-label prescribing must remain the exception to the rule and should be scrutinized and controlled by regulatory agencies using well-defined frameworks [43].

According to article 18 of law number 2011-2012, the physician is obliged to inform the patient that the prescription does not comply with the MA, that no suitable alternative medicine exists and that the off-label use may be associated with special risks. In addition, each off-label prescription must be marked as "off-label prescription" and has to be documented in the patient´s medical record [77],[81],[82].

MA holders are required to control off-label uses of their drugs by monitoring the adherence of prescriptions to the specifications defined in the MA (article L.5121-14-3 of the CSP). The ANSM must immediately be informed about unconventional off-label uses. A company may be obliged to implement measures for preventing and/or limiting the off-label use of drugs (e.g. specific information and trainings intended for prescribers). According to article L162-17-4-1 of the CSS (introduced by article 21 of law No. 2011-2012) such commitments may be included in agreements between the pharmaceutical company and the French Economic Committee of Health Products (CEPS). Failure to comply with these obligations may lead to a financial penalty against the company [80],[83].

5.2 RTU - General aspects

As stipulated in article L5121-12-1 of the CSP, off-label use is allowed in cases where an RTU is granted by the ANSM. By the possibility of issuing an RTU, also referred to as "waiver of MA specifications", the French health authority is provided with a regulatory framework for temporarily supervising the prescription of medicinal products for indications or conditions for which they are not yet licensed [38].

The conditions under which the ANSM may establish an RTU and the procedure for its implementation are specified in decree number 2012-742, dated 9th May 2012, which is related to article 18 of law number 2011-2012 [84]. In addition, a guideline was published by the ANSM in October 2012 in order to give a more detailed description of the general principles and requirements for issuing an RTU [38].

An RTU usually pertains to one pharmaceutical product but in case of generics or products having a similar mode of action several drugs may be involved. The RTU decision is issued a single time for any given drug prescribed in out- or inpatient settings and is valid for a maximum of three years. RTUs are necessarily accompanied by a monitoring protocol [38].

By opening a relatively long observation window, the benefits and risks of the unapproved drug usage can be assessed and new scientific information be collected [43]. The 3-year period of an RTU should be used by the manufacturer(s) to generate sufficient data for expanding the MA through usual procedures. Products for which an expanded indication is not granted within this period are considered as being not safe for off-label prescribing. As a consequence, the respective indication will no longer be permitted [78].

The "RTU guideline" clearly points out that RTUs are not substitutes for clinical trials. The data collected through the RTU surveillance program can supplement the MA dossier. However, controlled

clinical trials are considered as prerequisite for proving that a drug has a positive benefit-risk ratio and remain the reference procedure for receiving an MA extension [38].

Furthermore, RTUs should be distinguished from ATUs. In contrast to RTUs which can be applied to all medicines that have a national or centralized MA in France, ATUs are issued for innovative drug products which have not yet been granted an official MA and which are intended to treat serious or rare diseases for which no appropriate therapeutic alternative is available. ATUs provide early access to new promising treatments for which the benefit-risk ratio is presumed to be positive [86],[87].

Two different ATU types exist [88]:

- nominative ATU: issued for a named patient, at the request of and under the responsibility of the prescribing physician and
- cohort ATU: concerns a group of patients and is issued at the request of the holder of the licensing rights who commits to submit a MA application within a determined time period; participants of a cohort ATU are treated and monitored according to criteria defined in a protocol for therapeutic use and information collection.

5.3 RTU - process

The RTU process can be divided into the following stages: 1. Identifying the need of an RTU, 2. RTU assessment by the agency and 3. Announcing, implementing and monitoring of an RTU.

5.3.1 Identifying the need of an RTU

In principal, RTUs may be granted for all medicinal products, whether available in retail pharmacies or in hospitals. However, they are only elaborated by the ANSM when the following two conditions are met [38],[89]:

- **unmet therapeutic need**, i.e. there is no appropriate therapeutic alternative available (i.e. a medicine with a MA in France or a cohort ATU in the indication/population in question) **and**
- the **benefit-risk ratio** of the medicine is **assumed to be favorable** based on the available scientific efficacy and safety data.

The RTU process can be initiated by the ANSM when a situation of off-label use is identified. Furthermore, the following bodies are entitled to ask the ANSM to establish an RTU [38]:

- French Ministries responsible for Health and Social Security
- French National Authority for Health (*Haute Autorité de Santé*, HAS)
- Federation of National Health Insurance Funds (*Union nationale des caisses d'assurance maladie*, UNCAM)
- French Cancer Institute (*Institut National du Cancer*, INCA)
- Reference centers for rare diseases (*Centres of Expertise*) and
- approved patient associations.

All therapeutic needs reported by a learned society will also be considered by the French Health Authority as an alert for issuing an RTU.

It is important to note that pharmaceutical companies are not eligible for requesting an RTU. The ANSM guideline on "Temporary recommendation for use" clearly states that "[w]hen a situation in which a medication prescription does not comply with the MA is identified, the pharmaceutical company informs the ANSM and either:

- the situation is the result of a health need and the pharmaceutical company must therefore plan to submit an indication extension request or
- the situation is unjustified and it is the responsibility of the pharmaceutical company to inform the physicians of the inappropriate or even dangerous nature of such prescriptions." [38].

5.3.2 RTU assessment by the agency

After initiating the RTU process, the ANSM proceeds in the following successive phases: 1. Data collection, 2. Scientific assessment and 3. Decision.

5.3.2.1 Data collection

In the "Data collection phase" information is collected to assist the decision-making. The pharmaceutical company is requested to provide the ANSM within three months with all relevant information needed for assessing the efficacy and safety of the medicine in question in the intended clinical situation. This includes all clinical and non-clinical data, a list of all ongoing and planned clinical trials and their progress in France or abroad in the respective indication and an estimate of the number of French patients that may be affected by the RTU. In addition, the company has to send a draft patient monitoring protocol, a copy of any MAs granted in another country for this indication/conditions and, if applicable, a copy of any MA refusal or withdrawals and a copy of any scientific opinion issued by the EMA or any other competent authorities for the indication/condition in question. If several pharmaceutical companies are involved in the RTU process, the ANSM contacts each of them to acquire detailed information on the medicine [38].

In those cases where an RTU affects a rare disease, the ANSM further and simultaneously requests the opinion of the *Centres of Expertise*. In case of cancer, the INCA should be contacted to provide all relevant information. The same three-month period is applicable. The opinion should be based on the analysis of the need for an RTU, the efficacy and safety data available, and, if applicable, the research conducted by the reference center for the situation in question [38].

5.3.2.2 Scientific assessment

After receiving the requested information, an expert panel established at the ANSM starts with the assessment process according to the principles of scientific evaluation in medicine. Data from published clinical studies should be evaluated by peer review committees [38].

Several factors must be considered and carefully balanced by the expert panel before an RTU can be issued [38],[43]:

- The quality of the scientific evidence surrounding the drug and the proposed indication/condition: This evidence is crucial for issuing an RTU. Controlled studies will remain the gold standard for this purpose. In cases where only anecdotal evidence or poor quality studies exist, further clinical trials are required to provide stronger scientific evidence before an RTU can be granted.
- Drug safety: The state of knowledge of the drug (established vs. new medicinal product), the number and severity of adverse drug reactions, the risk in terms of drug interactions and potential harm in specific populations as well as the required treatment duration will be considered.
- Prognosis associated with a given disease: It is more likely that an RTU will be issued for a severe disease with a negative prognosis than for a mild one as the willingness to accept uncertainty with regard to the benefit–risk ratio is grater in the former case.
- Frequency of the disease occurrence: Randomized clinical trials remain the gold standard for drug development and approval. However, in some situation it is not possible to perform large clinical studies to develop evidence supporting new MA applications (e.g. rare diseases, special patient populations). The requirements for issuing an RTU have to be adapted accordingly.

5.3.2.3 Decision process

The ANSM determines the ratio between the presumed benefit and the potential risk. If the benefit-risk ratio is deemed favorable, a draft RTU is established. In case of an unfavorable benefit-risk ratio, the party requesting the RTU is informed about the negative outcome of the assessment. Whatever the outcome of the assessment, it will be published by the ANSM on the agency´s website [38].

An RTU contains information about the indication for which the exception is granted, the posology and route of administration, adverse effects and, if necessary, precautions for use, warnings and contraindications specific to the RTU framework. A hint should be given to the limited validity of the RTU and, if applicable, a new classification of the medicine for prescription and dispensing. Furthermore, the main scientific results supporting the soundness of the RTU should be presented [38].

The appendix of an RTU includes a patient monitoring protocol. Patient monitoring is an essential part of the RTU principle. It is required by law and is aimed at ensuring that the presumed benefit-risk ratio remains favorable. Patient monitoring should contribute to the safe use of the drug and should also encourage the pharmaceutical company to undertake clinical trials for obtaining a MA extension for the relevant condition/indication. The protocol contains a description of the data collection and patient monitoring process. At least one monitoring criterion should be defined that enables the assessment of the therapeutic benefit of the medicine. In addition, the process for collecting adverse effects and data with regard to the real conditions of use of the medicine should be described. The protocol also specifies the role of each involved party and the modalities and frequencies of sending the monitoring in-

formation to the ANSM in the form of periodic summary reports. At least two intermediate summary reports (1.5 years and 2.5 years) and a final report have to be provided [38].

It should be noted that the responsibility for patient monitoring within the scope of an RTU including its funding lies within the pharmaceutical company(ies). However, the patient monitoring can be delegated to a Centre of Expertise, provided that the medicine is used for the treatment of a rare disease. Failure to fulfill this monitoring obligation may lead to the suspension or withdrawal of the RTU [38].

An RTU may be accompanied by a draft agreement. This formal contract has to be signed by the company marketing the drug and the ANSM. It defines certain conditions the company has to comply with such as the modalities to be used for patient monitoring and follow-up, the efficacy and safety information that has to be collected, the real conditions of use, the schedule for reporting data to the agency and the role of people involved in monitoring [38],[90]. If necessary, the agreement may contain the pharmaceutical company's commitment to submit a MA extension application within a specified time frame. The "ANSM guideline" clearly states that "the agreement is bilateral and [..] cannot presume of the signature of the pharmaceutical company." [38]. It is therefore possible that an agreement is only signed by the General Director of the ANSM. In those cases, the modalities for data collection are established in the patient monitoring protocol appended to the RTU. However, in each case, the pharmaceutical company remains legally responsible for performing the monitoring. When the RTU concerns several pharmaceutical companies, a single agreement will be established that is applicable for all of them and the funding will be divided [38].

5.3.3 Announcing, implementing and monitoring of an RTU

As mentioned above, a draft RTU will be established when the data assessment results in the presumption that the benefit-risk ratio of the drug is favorable in the given indication/condition. The agency sends this draft RTU to the concerned pharmaceutical company(ies) and, if applicable, also the draft agreement. The pharmaceutical company has to sign the document within one month after receipt. This period may be expanded by one month upon request. At the end of the process, the ANSM's General Director signs the RTU and, if necessary, the agreement. The final decision of the ANSM will be published on the website of the agency.

The RTU and its updates are provided to the following parties: pharmaceutical company(ies), Minister for Health, HAS, UNCAM, CEPS and, if applicable, INCA and reference centers for rare diseases. By sending the RTU to professional bodies and learned societies, it should be ensured that any relevant information on the RTU (e.g. its implementation, any modifications, suspension or withdrawal) is forwarded to their members, i.e. physicians and pharmacists. It is postulated that by this means physicians are encouraged to become involved in the RTU process [38].

Within the framework of an RTU physicians must provide the patient with the following information [38],[80]:

- non-compliance of the prescription with the MA

- lack of appropriate alternative medicines
- description of the potential risks, the medicine's limitations and likely benefits and
- health insurance coverage of the prescription.

Physicians have to include the words "off-label prescription" on the prescription and must explain the reason for the prescription in the patient´s medical file. According to the modalities set forth in the monitoring protocol appended to the RTU, physicians are also obliged to collect and transmit monitoring data on their patients via monitoring form to the pharmaceutical company in question. Additionally, based on the general framework of pharmacovigilance, healthcare professionals are required to report any adverse events experienced by a patient to the appropriate regional pharmacovigilance center (CRPV) [38].

The pharmaceutical company is required to implement all monitoring processes as defined in the RTU. Beside this, the pharmaceutical company must comply with pharmacovigilance obligations including reporting of adverse reactions to the competent authority and notification of any new information that may affect the benefit-risk ratio of the drug. The company is responsible for ensuring that the medicine is prescribed in compliance with the MA or RTU. If deviations from the specified conditions are observed, the ANSM has to be informed and appropriate measures have to be undertaken by the company [38].

After granting an RTU, the ANSM is responsible for collecting and analyzing of all monitoring and safety data and for scrutinizing the development progress of the medicinal product, taking into account new available treatment methods. In the following situations, the ANSM is empowered to modify, withdraw or suspend an RTU [38]:

- public health risks associated with the drug usage
- failure of the company to fulfill the patient monitoring and information collection obligations
- provisions set forth by article L 5121-12-1 no longer being fulfilled (e.g. new therapeutic alternative available).

The ANSM informs all relevant bodies about its decision, especially in cases of emergency.

5.4 RTU - Promotion

As a general rule, pharmaceutical companies are formally prohibited from promoting medicinal products for any of its off-label uses. This also applies to the drug usages within the scope an RTU (article L.5122-3 of the CSP) [38].

Overall, law No. 2011-2012 strengthens the rules with regard to advertisement by introducing the obligation that promotional material has to be approved by the ANSM prior to its launch [81].

5.5 RTU - Reimbursement

According to article R163-8 et seq. of the Code of Social Security, off-label prescriptions are principally not reimbursed in France. The physician is required to mark a prescription which is outside the

scope of a MA as an off-label prescription. Article 18 of the Act (Loi n° 2011-2012) which completes article L. 162-4 of the CSS stipulates that this inscription applies to non-reimbursement, i.e. the costs have to be borne by the patient. However, some exceptions to this general rule exist when no alternative treatments are available, e.g. in case of medicinal products for which an ATU is issued by the agency or, in case of medicinal products prescribed for rare or some chronic diseases, when temporarily authorized for reimbursement by the HAS and ANSM (article L. 162-17-2-1 of the CSS; also called "article 56" model) [91].

Furthermore, article L. 162-17-2-1 of the CSS stipulates that medicinal products are by way of exception reimbursed for a limited time when the drug is subject to an RTU [94]. Once a "temporary recommendation for use" is granted, the Medicines Evaluation Commission (as part of the HAS) has three months to render an opinion on the reimbursement of the treatment [95].

Prior to the implementation of law number 2011-2012, medicinal products having a MA but used "off-label" in hospitals could be reimbursed if included in a specific list, called PTT (temporary protocol of treatment). This list was established by the Afssaps based on evidence-based medicine with participation of the National Cancer Institute and the HAS [92],[93]. In 2011, the agency performed 343 assessments and issued 64 PTTs. 32 off-label uses were judged as non-acceptable [92]. The PTT list will expire by the end of June 2014 [91].

5.6 RTU - Examples

It is postulated that the first RTUs are likely to be granted in the area of rare diseases, or in paediatrics, oncology or hematology [89]. However, so far, there is no RTU decision published on the ANSM website (last access on 21st October 2013).

Some reports dealing with RTU requests are published in the internet:

In January 2013, the association against AIDS (Aides) asked the ANSM to grant an RTU for Truvada (a combination of two anti-retroviral drugs already prescribed in France for people infected with HIV) as a preventive treatment of AIDS in people at risk. The benefit of Truvada for AIDS prophylaxis could be demonstrated in recent scientific studies. Additionally, it was emphasized that this indication has already been authorized for several months in the United States. In France, clinical studies are currently ongoing (Ipergay trial, *http://clinicaltrials.gov/show/NCT01473472*). The AIDS association considers that this indication meets a real need in France [96].

Baclofen (Lioresal) represents another medicine for which a "temporary recommendation to use" was applied for by a patient association (*Association Baclofène*). Baclofen was initially approved to treat multiple sclerosis but is largely diverted to treat alcohol dependence. As a result, the RTU request refers to the treatment of alcoholism . It is announced on the website of the Baclofen association that a "temporary recommendation for use" will be granted by the ANSM before the end of this summer. This statement is based on a presentation given by Dominique Maraninchi, Director General of the ANSM, at a conference (*colloque sur l'usage de ce médicament contre l'alcoolodépendance organisé*

à l'hôpital Cochin) in Paris on June 3rd. (*http://www.baclofene.org/baclofene/le-baclofene-autorise-contre-lalcoolisme*).

6. OTHER STRATEGIES FOR REGULATING OFF-LABEL USE

In the literature, several approaches for identifying, monitoring and controlling the off-label use of drugs have been proposed. Some of them have been already implemented by Member States. The following part is intended to provide an overview about different strategies.

6.1 Increasing transparency and information

For regulating the off-label use of medicines, it is essential to be comprehensively informed about the reasons and true dimensions of off-label prescribing. Such information is currently missing as the practice of off-label use is overall insufficiently documented. Therefore, several authors require more transparency in this field [10], [18],[19]. It is considered necessary to collect, document and evaluate data relating to off-label use. Based on the gathered information, relevant recommendations and policy decisions could be made. Enhanced transparency and information could help physicians to distinguish benign from harmful off-label uses [18].

It is proposed to establish a central register for off-label use administered by national or EU authorities [18],[19],[29]. The required information could be obtained from different stakeholders including pharmaceutical companies, health insurances, physicians and authorities [19]. However, when establishing such a register, property rights and patent claims, data protection issues, an additional administrative burden and the general limited willingness of physicians to report information on off-label prescriptions should be respected [19]. Furthermore, it may be questioned if such a register would be able to provide meaningful information about benefits and side effects as the generated data do not comply with fundamental scientific principles [29].

6.2 Monitoring of efficacy and safety of off-label use

Using medicines outside the specifications laid down in the label compromises patient safety [40]. This and the fact that off-label prescribing is extremely common make it necessary to systematically monitor treatment responses and adverse effects related to off-label use. Safety and efficacy information have to be collected and evaluated and measures to be taken in order to prevent risky and ineffective off-label prescribing [32]. However, monitoring in the off-label setting is challenging due to several reasons including the partly missing indication for usage in spontaneous case reports [2].

With the recent reform of the EU pharmacovigilance framework, the EU legislators aimed at addressing some of the deficiencies associated with off-label use of medicines, for example, by expanding the MAH´s responsibilities to drug applications outside the scope of the MA and by facilitating the reporting of suspected adverse reactions by HCPs and patients (see section 3.2 and 3.4). The new provisions may increase the knowledge of risks associated with off-label uses. Furthermore, the reform could generally contribute to a safer drug use as health authorities are now empowered to require MA hold-

ers to perform PASS or suspend, withdraw or vary MAs in case of safety concerns associated with off-label use. However, it remains to be seen whether doctors will be willing to report adverse drug reactions attributable to off-label prescribing [18].

6.3 Regulating off-label prescribing through HCPs

In general, physicians are empowered to prescribe medicines off-label but they have to take their decision carefully. However, studies show that a high number of drugs is prescribed in the absence of solid evidence. It is criticized that physicians often rely on experiences, anecdotal reports and key opinion leaders to guide their treatment decisions (see section 2.4). Furthermore, some published studies indicate a failure of practitioners to recognize that a prescription is off-label [75]. On the one hand, this may be due to the fact that the scope of the term "off-label use" is not clearly defined. Therefore, it is required to find a harmonized and clearly formulated definition. On the other hand, physicians are often not fully informed about the characteristics of a drug. A possible strategy to improve the quality of off-label prescribing would be to increase the knowledge of HCPs by independent educational programs. It is reported that some MSs have already established tools to effectively communicate relevant data on drug uses to physicians [75].

As it is considered important to provide physicians with the latest accurate and non-misleading information on a medication, some authors are in favor of allowing MA holders to disseminate information on off-label use (e.g. peer-reviewed materials and educational programs) [32]. This measure could improve the prescription behavior of physicians. However, the information provided by manufacturers is often not independent and may be of less quality [32]. There is a high risk that pharmaceutical companies may use such a tool for illegal promotional activities.

Another strategy to secure the safe use of drugs could be to restrict off-label prescriptions to physicians with an appropriate qualification (for instance, the European Society for Medical Oncology (ESMO) exam for oncologists) [29]. Alternatively, the permission to issue an off-label prescription could be limited to specialized treatment centers [29].

Some authors believe that the off-label use problem can only by solved by "placing the responsibility […] squarely on the shoulders of physicians" [44]. It is for example postulated that reinforcement of the physician's liability for off-label uses would be an effective measure [25]. Theoretically, such a "liability threat" could reduce the demand for off-label uses by physicians with the consequence that manufacturers invest in extensions of drug approvals.

6.4 Establishing of lists of acceptable off-label applications

It is recommended to work out lists of acceptable off-label uses to provide physicians with a guide before prescribing a drug outside the scope of the MA. Such lists are already in place in some countries and some authors call for a harmonized EU wide solution [28]. In the U.S., selected, evidence-based off-label uses are included in "standard medical compendia" [28]. However, it is criticized that rec-

ommendations provided in such medical guides are often lacking in consistency, quality and transparency [32].

Gazarian et al. (2006) describe a very interesting approach for increasing the quality and safety of off-label prescriptions by establishing a guidance to help physicians judging the appropriateness of an off-label use [23]. They differentiate three categories of off-label prescription: routine (justified by high-quality evidence), use within the context of formal research and exceptional use (justified by individual clinical circumstances). For each category, the process for decision making and consequential measures (e.g. informed consent procedure) are described.

In some countries expert panels have been established in order to perform a scientific evaluation of off-label uses in selected indications. Certainly, such expert panels can provide useful clarifications for some off-label issues. If an evaluation for instance indicates that the off-label uses of a drug is not supported by solid evidence, the manufacturer is obliged to take position either by providing scientific data for substantiating a MA extension or by highlighting the off-label use as a contraindication in the label [19]. Nevertheless, the evaluation process by expert panels is extremely labor-intensive and time-consuming and the number of drugs and indications that would have to be reviewed is extremely high. Therefore, it is unlikely that this strategy is feasible to control the widespread and rapidly evolving off-label use problem [8], [29],[40]. A possible solution would be to limit the review process to products that are both risky and expensive as proposed by Gillick (2009) [40]. She motivates her suggestion by arguing that "[m]edications with few side effects and low cost may not warrant regulation when used off-label unless they are so widely prescribed that the population-level risk is high."[40].

In the UK, a new tool, called ESUOM (evidence summaries: unlicensed and off-label medicines) has been recently introduced by the National Institute for Health and Care Excellence (NICE). ESUOMs provide a summary and critical review of the best available evidence for selected off-label drugs that are considered to be of significance. The summaries are aimed at supporting the decision-making on the use of an off-label medicine when no appropriate licensed alternative is available. However, it is emphasized that the summaries do not constitute formal NICE guidance [97]. Despite its short existence, already 21 ESUOMs have been published on the NICE website and ten further ESUOMS are pending (*http://www.nice.org.uk/mpc/evidencesummariesunlicensedofflabelmedicines/home.jsp*).

6.5 Influencing the reimbursement of off-label use

The reimbursement of drugs prescribed off-label depends on local regulations. It is claimed that more rigorous policies on reimbursement of off-label uses might influence the prescription behavior of physicians [18],[19],[32]. In Germany, reimbursement is restricted to those off-label indications that are included in the Pharmaceutical Directive (see section 3.3). However, it seems as if this strategy does not really affect the number of off-label prescriptions in Germany. On the one hand, this may be due to the fact that the number of indications evaluated by the "BfArM off-label panels" is very low. On the other hand, in case of uncertainties or if the health insurance does not bear the costs of the off-label

use, physicians are advised to expose a private prescription at the expense of the patient. Furthermore, the reimbursement restriction does not apply to private health insurances. This situation may lead to unequal treatments of patients.

Another instrument that could have a sustainable effect on the off-label situation is "coverage under evidence development". This tool links the reimbursement of the off-label use to the requirement that the patient participates in a registry or clinical trial testing that use (preferably a clinical trial) [98].

6.6 Promotion of research

Innovative off-label use may potentially lead to the discovery of new therapeutic options. Nevertheless, it is required to confirm the efficacy and safety of the new use in formal studies. Also in cases where the off-label use develops without adequate evidentiary support or is related to potential risks for the patient manufacturers should be urged to sponsor the needed research [32]. The ultimate goal of these studies should be to get the off-label use in the label through official HA approval or, in case of safety/efficacy concerns, to issue an appropriate warning and prevent further off-label prescribing. The main question in this context is how to organize, fund and conduct such "off-label use researches". Usually, the whole responsibility for a medicinal product including post-marketing developments lies with the MA holder. However, especially in case of off-patent drugs and/or small target populations, the pharmaceutical industry has little economic interest in investing in expensive clinical trials. In these situations, it may be necessary to support research on off-label uses by the government or other noncommercial organizations [32]. Some authorities have already adopted such measures. The EMA for instance encourages studies into off-patent drugs essential for paediatrics [99].

In addition, more support for academic clinical studies initiated by the researcher themselves (investigator-initiated trials) should be provided. Already existing instruments such as health service research and therapy-optimization studies should further be used to improve the knowledge about off-label uses and its outcomes [4].

6.7 Changes in drug regulations

The drug approval process is very laborious, time-consuming and expensive. As it is not possible to supply standard data sets with hundreds of patients in distinct diseases (e.g. rare malignancies), it is proposed to lower the level of significance or power for granting a MA [3],[44]. Less rigorous studies should be required for off-label indications compared to the primary indication [98]. The present knowledge as well as any open questions could be addressed in the label [3],[32]. These measures could lead to an increase in the number of approvals and, in the following, to a sustainable reduction of off-label uses.

Especially in oncology, a high number of off-label prescriptions are observed. This is partly due to the fact that indications of new approved drugs are very narrowly defined (see section 2.3). To address this, it is suggested to approve less specific indications and dose regimens for new drugs [3]. To en-

sure close observation, adverse event monitoring and quality control of these drugs a restriction in the label such as "use only in quality controlled phase III trials" could be adopted [3].

Currently, only the MA holder is empowered to decide whether to bring a new agent onto the market or to extend an existing MA. Therefore, it is proposed to implement official procedures that also allow medical societies to initiate label changes, e.g. based on evidences obtained from investigator-initiated trials [3]. Another strategy could be to force pharmaceutical companies to seek supplemental drug approvals as soon as sufficient data are available supporting the selected off-label use. However, such an approach would mean an encroachment on entrepreneurial freedom [8].

6.8 Creating incentives for pharmaceutical companies

The best way for controlling the off-label use of medicines would be to get as many off-label applications as possible approved. However, manufacturers are often not interested in sponsoring research on pharmaceutical products when the patent protection is expired and the products are already widely prescribed off-label. The same applies to products for small populations and rare diseases. Therefore, making the expansion of approved drug labels more attractive to manufacturers could be a useful strategy for reducing the number of off-label prescriptions.

The European legislators have already created some incentives in order to encourage the further development of already authorized medicinal products including an extra one-year market protection for new therapeutic indications for products under protection or a non-cumulative period of one year of data exclusivity for already established products (see section 4). However, the high prevalence of off-label prescribing clearly indicates that the existing incentives are not sufficient to solve the situation. Therefore, some authors propose clearer and more comprehensive incentives to authorize new indications [18],[19],[32]. However, other authors believe that such a strategy would not necessarily persuade pharmaceutical companies to undertake the corresponding investments [25].

Off-label use is often seen in patients suffering from rare diseases. The purpose of the "Orphan Drug Regulation" is to improve the development of medicines for orphan diseases by providing incentives for the pharmaceutical industry. Since its implementation, a high number of "orphan drugs" has been approved and it is expected that the number will further increase. Accordingly, it can be concluded that this regulatory instrument, at least in part, will contribute to a reduction of off-label use in this medical field.

One of the explicit objectives of the "Paediatric Regulation" is to reduce the off-label use of medicinal products in the paediatric population which is estimated to reach values of up to 90% in neonatal care. To achieve this goal, both, obligations and rewards/incentives were implemented in the EU. Based on a recently published report, the number of medicines approved for children increased during the last years. However, up to now only one PUMA has been approved (see section 4). Hence, it can be argued that the off-label use of "well-established" products cannot be solved by the "Paediatric Regulation".

6.9 Regulating off-label promotion

Off-label promotion is prohibited in the EU. Nevertheless, illegal off-label promotion practices are commonly observed. Therefore, it is hypothesized that more rigorous prosecutions and an increase in penalties could result in a reduction of illegal advertisement and, consequently, in a slower increase of off-label prescribing [100]. However, experiences gained over the last years in the U.S. indicate that deterrence as a strategy for altering the marketing practices of pharmaceutical companies with regard to off-label use does not work [100]. This is attributed to the fact that "[…] the fines and associated legal costs pale in comparison to the profits made by companies convicted of the crime." [44].

7. DISCUSSION

In the previous chapters it could be demonstrated that the off-label use of medicines is very common and that it may be associated with an increased risk for the treated patient. The off-label use phenomenon is neither restricted to special clinical situations nor to single countries. It can be considered as an international problem with comparable frequencies reported in Europe and North America [3]. There are situations where off-label prescribing is considered to be of significance, especially when no licensed medicines for the condition or the proportion of people requiring treatment exist. However, due to safety and efficacy concerns off-label prescribing should be regarded as an exemption from the rules.

Before a medicinal product is placed on the European market, it has to have undergone a stringent approval process. This is to ensure that the drug is safe, effective and of high quality. Off-label prescribing is beyond the control of the health authorities. Therefore, it is claimed that "[…] general off label use of drugs is the death of the idea of regulation" and that "the widespread off label use of drugs in 50–100% of a patient population is a declaration of bankruptcy" [3]. As a consequence, more, not less regulation is needed to prevent that patients are exposed to significant risks when using medicines outside the terms specified in the MA [3].

There are no harmonized rules existing at EU level. Instead, every MS has its own policy with regard to off-label prescribing and reimbursement [54]. These rules are often unclear and insufficient to solve the off-label use problem. Accordingly, there is a call for improving and aligning the existing country-specific regulations [28].

In December 2011, the French legislator introduced a new regulatory framework (law number 2011-2012) aiming at strengthening the safety of medicines. The reform resulted from a serious drug scandal involving Mediator®, a medicine which was also prescribed off-label as a weight-loss aid. Mediator® could be held responsible for hundreds of deaths resulting from drug-induced heart valve damages. With the new law and its related decree, France fundamentally changed the way how to regulate and monitor off-label use of medicines. Prior to the reform, off-label use was not subject to rigorous legal restrictions. It is stated that off-label use of drugs was in a "grey zone" but now it is "brought into the light" [90].

In principle, the new law recognizes the importance of off-label uses in some medical fields and allows physicians to prescribe drugs for indications or conditions not covered by the MA. However, no authorized alternative may be available in France. In addition, an RTU has to be granted for that use or the treatment has to be considered essential by the physician. An RTU is issued by the ANSM for a period of three years if there is an unmet therapeutic need and the benefit-risk ratio of the drug use is assumed to be favorable. RTUs are generally not restricted to rare or chronic diseases.

The amended French law gives the off-label use of medicines a legal framework. By establishing a new kind of MA, the legislator tries to regulate this uncontrolled field of medical practice. Beside the RTU, also other measures were introduced by the reform that may also be relevant in this context.

The previous chapter of this thesis described some further meaningful strategies for regulating the off-label use of drugs (see section 6). In the following, it will be discussed whether those or similar approaches have also been integrated in the French "off-label framework".

- Increasing transparency and information

A pivotal issue for controlling the off-label use of medicines is the transparency of drug prescriptions. Only if there is an adequate awareness of the off-label uses of a drug, relevant recommendations and policy decisions can be made (see section 6.1).

The French law is aimed at improving the transparency of off-label prescribing. Each physician is legally required to adequately inform the patient about an off-label use and to document the prescription in the patient´s medical record. Pharmaceutical companies have to inform the ANSM when prescriptions deviating from the MA are identified [38]. As soon as an RTU is issued, transparency is guaranteed through the specified rules.

Furthermore, the ANSM is required to implement an administrative and scientific database concerning illnesses, treatments and how to make good use of drug products with the collaboration of the National Health Authority and the UNCAM [77]. This tool may also be helpful in identifying and evaluating off-label uses of drugs.

All these measures lead to the expectation that the knowledge about off-label prescriptions will increase in the future. However, Le Jeunne et al. (2013) claim that more far-reaching measures are required. They suggest cross-referencing of all available databases (e.g. by using the shared computerized patient file) for identifying all off-label prescriptions occurring in France [91].

- Monitoring of efficacy and safety

Off-label use lacks rigorous and thorough scientific scrutiny and may therefore be associated with an increased risk for the patient. Therefore, monitoring of efficacy and safety of the drug use is extremely important. The EU already addressed this issue with the last update of the pharmacovigilance framework (see section 3 and 6.2).

Pharmaceutical companies that commercialize a medicinal product in France are responsible for controlling off-label prescribing. According to article L.5121-14-3 of the French Public Health Code, they must contribute to the good use of drugs by ensuring that the medicines are prescribed in compliance with their MAs or RTUs. The ANSM has to be informed about any unconventional prescribing practices and the MA holder is obliged to take all appropriate measures to prevent further off-label uses. Breaches of these duties can lead to a fine by the ANSM or by the CEPS. The latter applies if an agreement has been signed between the CEPS and the drug company regarding the management of off-label prescriptions (see section 5).

Monitoring of efficacy and safety of drugs used outside the terms of a MA is one of the key elements of the RTU system. An RTU provides a relatively long observation window in which the benefits and risks of an off-label use may be collected and evaluated. The pharmaceutical company is required to implement patient monitoring procedures according to the protocol described in the appendix and/or agreement of the RTU. In addition, responsibilities of the physicians are described. The safe use of a drug is ensured through data collection and reporting and through routine pharmacovigilance activities. The ANSM has to be immediately informed about any new information that may affect the benefit-risk ratio of a drug. In case of non-compliance or if the data indicate a risk for the patients, the authority can modify, suspend or withdraw the RTU.

Hence, the French RTU system is aimed at making the off-label use of drugs safer by strengthen its monitoring and control.

- Regulating off-label prescribing through HCPs

Although some authors propose to strengthen the responsibilities of physicians in order to control the off-label use of drugs (see section 6.3), the new off-label framework in France gives the physician a rather limited role [83]. Within the scope of an RTU, physicians are required to provide the patient with comprehensive information about the off-label use, including risks, limitations and likely benefits (see section 5.3.3). They have to indicate the off-label use on the prescription. Furthermore, physicians have to collect and transmit all monitoring data on their patients to the MA holder in question. The physician's responsibilities are set forth in the monitoring protocol of the RTU. It can be assumed that the liability of physicians is overall reduced when treating a patient according to the specifications laid down in the RTU.

To ensure compliance of the HCPs all relevant information regarding the RTU (e.g. establishment, withdrawal etc.) shall be forwarded to the HCPs by professional bodies or learned societies.

- Establishing of lists of acceptable off-label applications

Lists of acceptable off-label uses may be a meaningful tool for improving the quality and safety of off-label prescriptions. There are already lists/guides existing in several countries. However, due to the high number of off-label prescriptions it will be difficult to establish recommendations for each potential off-label use. Therefore, it is advisable to restrict the lists for example to "high-risks" drug uses (see section 6.4).

In France, each RTU decision will be published on the agency website and transmitted to the relevant bodies and institutions. Prior to the reform of the French law, the former health authority Afssaps (in collaboration with the INCA and HAS) established a list of off-label indications that are reimbursable in hospital settings (PTT). However, this PTT list will expire in 2014 (see section 5.5).

- Influencing the reimbursement of off-label use

It is postulated by some authors that more rigorous policies on reimbursement of off-label uses might influence the prescription behavior of physicians (see section 6.5).

In France, off-label prescriptions are principally not reimbursed. Each physician is legally obliged to write "off-label" on all prescriptions that are outside the terms of the MA indicating that the drug is not reimbursable. As a consequence, the costs have to be borne by the patient. However, an RTU may result in a right to reimbursement for the drug for the designated indication (see section 5.5). In this context, it is criticized that the requirement set forth in article 18 of the Act (inclusion of a special wording on off-label prescriptions) also applies to RTU prescriptions. This could be problematic insofar as it may create confusion for social security institutions with regard to reimbursement [83]. Other authors argue that HCPs will not necessarily comply with this requirement. This is due to the fact that prescriptions cannot be controlled by pharmacists dispensing the drug or the Social Security responsible for reimbursement as they usually do not know the diagnosis (or targeted indication) of the treatment [91]. Hence, this strategy is not suitable for identifying off-label prescriptions and increasing the transparency.

Prior to the reform, off-label prescriptions could be reimbursed in France when included in the PTT list or, in case of rare and some chronic diseases, when temporarily authorized for reimbursement by the French drug agency and the HAS (see section 5.5).

- Promotion of research

"Off-label use research" is important to verify the efficacy and safety of new drug uses. It was claimed by some authors that RTUs are able to promote the development of new indications/conditions of use [43]. On the one hand, the data collected through monitoring of patients treated within the scope of an RTU could provide a good basis for initiating a clinical trial. On the other hand, pharmaceutical companies can be obliged to submit an extension of the MA in a predefined timeframe (specified in the agreement associated with the RTU).

However, it is criticized that the 3-year period of an RTU is too short for generating reliable data in order to file a MA application [91]. A possible solution could be to create a "renewable RTU", meaning a one-time prolongation of the RTU for three years. In cases where this additional time is not sufficient to receive the necessary data (e.g. small patient population), a temporally unrestricted "use recommendation" (UR) could be drafted, provided that there is an unmet medical need. An UR should be accompanied by a patient follow-up and should regularly be re-assessed to guarantee the save use of the product [91].

- Changes in drug regulations

In order to increase the number of MA extensions/amendments it is proposed to lower the level of significance laid down by health authorities (see section 6.7).

The off-label use framework recently implemented in France does not pursue such a strategy and requires controlled clinical trials for proving that a drug has a positive benefit-risk ratio. In this context, the "RTU guideline" clearly states that the data collected within the scope of an RTU are only suitable to supplement the MA application. They cannot replace clinical studies (see section 5.3.2).

Another approach aims at forcing pharmaceutical companies to apply for a MA extension as soon as sufficient data are available supporting the selected off-label use. The new French law partly addresses this tool. On the one hand, an RTU may be accompanied by an agreement containing the pharmaceutical company's commitment to apply for an extension of an indication or a modification of the MA within a specified time frame. On the other hand, a pharmaceutical company is required to submit an indication extension request when an off-label use is identified which is the result of a health need. If the company fails to comply with this requirement, measures have to be undertaken in order to prevent the further off-label use of the drug.

- Creating incentives for pharmaceutical companies

France's new framework for regulating off-label uses of drugs does not provide any financial incentives for pharmaceutical companies to comply with the conditions laid down in the RTU. This is considered as a disadvantage by some authors [90].

However, a possible incentive for manufacturers may be that an RTU may result in a right to reimbursement. Furthermore, it is likely that an RTU lead to an increase in popularity of the respective drug and its related off-label use. This should also be of relevance for pharmaceutical companies.

Nevertheless, an RTU carries with it several duties and responsibilities. The MA holder has to bear the costs of patient monitoring and follow-up measures and is responsible for implementing the procedures as stipulated in the RTU even if an agreement is not signed. Furthermore, it can be expected that the MA holder will be held liable for any harm caused by a drug within the scope of an RTU. Therefore, it is questionable whether MA holders will be willing to provide all necessary data for evaluating the benefit-risk ratio of an off-label use in the context of an RTU.

In the light of the above it could make sense to provide further incentives. Le Jeunne et al. (2013) propose to simplify the requirements for getting a MA extension when an RTU is granted (for example, by submission of data collected through the RTU program in combination with literature data instead of clinical study data) [91].

A further measure could be to involve the pharmaceutical company in the RTU initiation process. The right to initiate an RTU evaluation combined with other incentives could make the RTU system more attractive for manufacturers and contribute to an increased transparency and safety of off-label prescriptions.

- Regulating off-label promotion

In France, manufacturers are not allowed to promote a medicinal product for any of its off-label uses. This also applies to RTUs (see section 5.4).

Overall, the new French legislation strengthened the control of advertising. Promotional material aimed at healthcare professionals must now be authorized *a priori* by the ANSM (so-called "advertising visa") [81]. By this measure, the health authority will be enabled to curb illegal promotional activities including those for off-label uses.

It can be summarized that the new off-label framework established in France pursues several approaches generally proposed for regulating and reducing the off-label use of drugs. According to Emmerich et al. (2013), this comprehensive reform "deserves to be discussed". They highlight the importance of the RTU process and argue that it could potentially be extended to the European Union and other countries [43].

The main advantages of the RTU system including the other introduced measures are:

- increased transparency of off-label prescriptions
- comprehensive evaluation of risks and benefits of off-label uses by the ANSM
- precisely defined monitoring and reporting procedures
- the possibility to force pharmaceutical companies to apply for MA extensions and
- the possibility to take appropriate measures in case of any safety concerns.

Accordingly, the new off-label framework established in France will likely contribute to a tighter control and an increase in the overall knowledge and safety of off-label prescriptions in France. It is also postulated that the RTU-based system may lead to an equitable access to medicines and that it could facilitate and promote the development of new indications [43].

However, the new policy has some drawbacks. First of all, the standards for issuing an RTU are not clearly defined, either in the "RTU decree" or in the "RTU guideline". Furthermore, some authors fear that the new framework for regulation the off-label use in France could lead to a bottleneck, especially in situations of high medical need (e.g. rare diseases) [90]. This is due to the fact that the process for obtaining an RTU is highly bureaucratic. Based on the high number of off-label prescriptions, it is questionable if the ANSM will be able to evaluate all incoming RTU requests. In addition, timelines for the risk-benefit evaluation performed by the ANSM are not clearly defined in the guideline. This could lead to delays in the RTU approval process. In this context, it should be highlighted that until today (almost 1.5 years after publication of the "RTU decree"), no RTU approval has been published on the agency´s website.

The RTU system focuses on "medically justified" off-label prescriptions for which the benefit-risk ratio is assumed to be favorable. Therefore, only a small proportion of off-label uses will be covered by this approach. In order to control the widespread off-label phenomenon it is proposed to establish an "off-label committee", composed of members from different institutions and organizations (e.g. HAS,

ANSM, CRPV and UNCAM). The responsibility of such a joint "off-label committee" could be to monitor and control all off-label situations, not only those covered by the RTU framework [91].

According to the French law, manufacturers have to prevent off-label uses outside the scope of an RTU unless the off-label use is scientifically justified and the MA holder is seeking for an amendment of the MA. However, there are many off-label prescriptions that are considered essential although the conditions for issuing an RTU are not fulfilled. It would not be in the patient's interest to curb all of them. Therefore, it is suggested to limit the review process to risky and expensive drugs or to drugs without high-quality evidence and to allow "appropriate off-label uses" [23],[40]. According to Le Jeunne et al. (2013), the kind of response to an off-label use should be depending on the scientific proof of the treatment and the real medical need [91].

One further disadvantage of the RTU approach was pointed out by Emmerich et al. (2012) [43]. They argue that a new drug use that has been temporarily authorized by the ANSM will probably be further prescribed after expiry of the 3-year period of an RTU, even if a new MA or MA extension is not granted by the ANSM. This could be of relevance in situations where safety or efficacy concerns were detected.

In summary, the French approach may be considered a valid contribution to regulate off-label uses of drugs. However, further progress should be made.

8. CONCLUSION AND OUTLOOK

Off-label prescribing of medicines is a widespread medical practice that is neither restricted to special clinical situations nor to single countries. The reasons for using a drug outside the specifications laid down in the label are diverse and complex. In certain situations, off-label use of drugs is justified on several grounds (e.g. to fulfill a public health need not covered by an existing MA). However, off-label use lacks rigorous and thorough scientific scrutiny. Therefore, it poses enormous unknown risks to the patients. Accordingly, off-label prescribing should be regarded as an exception to the rules and measures should be undertaken for its identification, monitoring and control.

The European legislation does not directly regulate the practice of off-label prescribing. Instead, MSs have established their own policies. These rules are often unclear and generally insufficient to solve the off-label use problem. Consequently, there is a call for improving and harmonizing the existing rules and systems.

With implementation of law number 2011-2012, the French legislators fundamentally changed the way how to regulate and monitor the off-label uses of medicines. The reform provides France with a new kind of MA, called "recommendation of temporary use" (RTU). The RTU system together with other introduced measures tightens the identification, monitoring and control of off-label prescriptions and may contribute to an overall safer use of medicines outside the scope of the MA. It is also postulated that the RTU framework may facilitate and promote the development of new indications.

However, despite some obvious advantages, this approach has some drawbacks. Among others, it is criticized that the RTU process is laborious and time-consuming. RTUs focus on “medically justified” off-label uses. Therefore, only a small proportion of off-label prescriptions will be covered by this strategy. Furthermore, it is assumed that the measures are not far-reaching enough to increase the transparency of off-label prescriptions and to ensure that the different stakeholders comply with the conditions laid down in the RTU. It is also claimed that the RTU period of three years is too short to collect sufficient data for obtaining a MA extension. Consequently, there is a high need to improve this system, for example by

- cross-referencing available databases for increasing the transparency of off-label prescriptions
- establishing an “off-label committee” responsible for all off-label applications
- providing a more detailed guidance for the RTU evaluation process (including timelines for the ANSM)
- providing incentives for pharmaceutical companies to comply with RTU requirements
- implementing the possibility for a second RTU period and, if required, a temporally unrestricted “use recommendation”
- restricting the control to specific off-label uses and permitting those which are harmless and effective.

Several other approaches to identify, monitor and control the off-label use of medicines have been proposed in the scientific literature. They aim at increasing the transparency and monitoring of off-label uses and at influencing the prescription behavior of HCPs, the post-marketing strategies of manufacturers and/or the reimbursement policy of health insurances. Furthermore, it is suggested to create incentives for manufacturers, to promote off-label research, to change the rules for off-label promotion and/or to adapt drug regulations. Some of these approached deserve to be discussed; others were already implemented by MSs (e.g. increased monitoring based on the "EU Pharma Package” or promoting the development of drugs for orphan diseases and paediatrics). However, so far none of these strategies is suitable to sustainably curb the common practice of off-label prescribing.

It can be concluded that only a combination of various strategies will likely be able to solve the widespread off-label use problem. To ensure access to high-quality and safe medicines for the entire EU population it is required to find an EU-wide harmonized solution.

9. EXECUTIVE SUMMARY

Before a medicinal product is placed on the European market, it has to have undergone a stringent approval process. This is to ensure that the drug is safe, effective and of high quality. The usage of an authorized medicinal product outside the terms of its marketing authorization (MA) is internationally described as off-label use.

Off-label use of medicines is a widespread medical practice which is neither restricted to special clinical situations nor to single countries. There are situations where off-label prescribing is considered to be of significant value (e.g. to fulfill a public health need). However, due to the lack of rigorous and thorough scientific scrutiny drug usages outside the scope of the MA may be associated with potential harm to patients. Accordingly, off-label prescribing should be regarded as an exception to the rules and measures should be undertaken for its identification, monitoring and control.

Off-label use is challenging for the various stakeholders including regulatory agencies, health care professionals, pharmaceutical companies, health care payers and consumers.

There are no harmonized rules existing at EU level. Instead, each MS has its own policy with regard to off-label prescribing and reimbursement. Some countries have already implemented strategies in order to curb the widespread off-label use of medicines. However, these measures do not seem to be able to adequately address the problem.

The French authority approach may serve as an example of such local regulation. In December 2011, the French legislator introduced a new regulatory framework (law number 2011-2012) aiming at strengthening the safety of medicines. Based on this reform, France fundamentally changed the way how to regulate and monitor the off-label use of drugs. Among others, a new kind of marketing authorization, called “recommendation of temporary use” (RTU) was introduced. RTUs may be temporarily granted for an off-label use if there is an unmet therapeutic need and the benefit-risk ratio of the intended use is assumed to be favorable. Key elements of RTUs are strict monitoring of efficacy and safety of the drug use in question, a possible commitment of the pharmaceutical company to submit an application for a MA extension within a specified timeframe and a high likelihood for reimbursement. The RTU system together with other introduced measures tightens the identification and control of off-label prescriptions and may contribute to an overall safer use of medicines outside the scope of the MA. However, beside these advantages, the new framework has also some drawbacks. One of the main problems is that RTUs only focuses on “medically justified” off-label prescriptions. Therefore, only part of off-label uses will be covered by this approach. Overall, this new strategy is not expected to be comprehensive enough to adequately address the off-label issue and further progress should be made. Nevertheless, it can be considered a valid contribution to regulate the off-label use of drugs.

In the literature, several other approaches for regulating the off-label use of medicines have been proposed. They are summarized and discussed in this master thesis.

It can be concluded that the regulatory rules with regard to off-label use require an improvement not only in France, but also in the European Union and other countries. It is likely that only a combination of various strategies will be able to solve the widespread off-label use problem. To ensure access to high-quality and safe medicines for the entire EU population an EU-wide harmonized solution is needed.

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