

# TOWARDS A BETTER MANAGED OFF-LABEL USE OF DRUGS





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## LIST OF ABBREVIATIONS

<b>ABBREVIATION</b>	<b>DEFINITION</b>
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ABGB	Allgemeines bürgerliches Gesetzbuch
ÄG	Aktiengesellschaft
AIDS	acquired immune deficiency syndrome
AIFA	Italian Medicines Agency
AMD	age related macular degeneration
ASCO	American Society of Clinical Oncology
BCFI	Belgian Centre for Pharmacotherapeutic Information
BfArM	Das Bundesinstitut für Arzneimittel und Medizinprodukte
BRAMD	Bevacizumab Ranibizumab Age-related Macular Degeneration
BS	Belgisch Staatsblad (Belgian Official Journal)
BSG	Bundessozialgericht
CATT	Comparison of Age-related Macular Degeneration Treatments Trial
CCGs	Clinical Commissioning Groups
CEPS	Health Products Economic Committee
CHMP	Committee for Medicinal Products for Human Use
CJEU	Court of Justice of the European Union
CMS	concerned member states
CTG/CRM	Commission for reimbursement of pharmaceuticals
CVZ	College voor zorgverzekering
DBC	Diagnose behandeling combinatie
DPR	direct patient reporting
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EUCOPE	the European Confederation of Pharmaceutical Entrepreneurs
EU	European Union
EUROPABIO	European Association for Bio-Industries
FAMHP	Federal Agency for Medicines and Health Products



FCA	False Claims Act
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
GBA	Joint Federal Committee of Physicians Dentists, Hospitals, and Health Insurance Funds
GMC	General Medical Council
GYEMSZI	National Institute for Quality and Organizational Development in HealthCare and Medicine (Hungary)
HERA	Herceptin Adjuvant
HIV	Human immunodeficiency virus
HMG	Heilmittelgesetz (Swiss Federal Law on medicinal products and medical devices)
IFR	Individual Funding Requests
IGZ	Dutch Healthcare Inspectorate
IGZ	Inspectie voor de Gezondheidszorg
INCA	Institut National du Cancer
IVAN	Age-related Choroidal Neovascularisation
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
MFC	Medico-Pharmaceutical Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Member State
NCA	the Italian National Competent Authority
NGS	Next Generation Sequencing
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHDI	National Institute for Health and Disability Insurance
NSW	New South Wales
PDCO	The Paediatric Committee



PFDA	provincial food and drug administration
PHC	Public Health Code
PIP	paediatric investigation plan
PLD	Product Liability Directive
PSUR	Periodic Safety Update Report
PTAC	Pharmacology and Therapeutics Advisory Committee
PTU	protocol for therapeutic use
PUMAs	Pediatric-use marketing authorizations
R&D	Research and development
RCT	Randomised clinical trial
RD	Royal Decree
RDRD	Rare Disease Repurposing Database
RIVM	Nederlands Rijksinstituut voor volksgezondheid en milieu
RIZIV/INAMI	Rijksinstituut voor ziekte-en invaliditeitsverzekering – Institut national d'assurance maladie-invalidité
RMS	Reference Member State
RTU	Recommandation Temporaire d'Utilisation
SABCS	San Antonio Breast Cancer Symposium
SARS	Severe Acute Respiratory Syndrome
SGB V	Sozialgesetzbuch
SmPC	Summary of Product Characteristics
SPC	Supplementary protection certificate
SSAEs	Serious systemic adverse events
SSF	Special Solidarity Fund
StGB	Strafgesetzbuch
TAU	Temporary authorization for use
TEU	Treaty on European Union
TFEU	Treaty on the Functioning of the EU
TRIPS	Trade-Related Aspects of Intellectual Property Rights



TRU	Temporary recommendation of use
UK	United Kingdom
UNCAM	Union nationale des caisses d'assurance maladie
US	United States
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
WTO	World Trade Organisation
ZiNL	Zorginstituut Nederland
ZonMw	Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie



## ■ SCIENTIFIC REPORT

### 1 INTRODUCTION

#### 1.1 Background and scope of the report

**Drug marketing and prescription in Europe is based on the idea of prior registration of the medicinal product**, where this registration relates to named and specified indications and modalities of use (age category, indication, dose, dose interval, route of administration). The marketing authorisation is granted after establishment of the balance between benefits and risks following an assessment of quality, safety and efficacy by the competent regulatory authority. Registration is based namely on the evaluation of the safety and efficacy of the treatment for the listed indications and modalities of use, mainly through clinical trials. Since the **marketing authorisation is based on the content of the dossier that is submitted to the authorities by the applicant**, an indication or a modality of use that is not claimed by the applicant will not feature in the package insert, unless it is listed as a contraindication or warning.

**Off-label use is the use of a medicinal product for another indication, another patient group, another dose, dose interval or by another route of administration than indicated in the package insert.**<sup>1</sup> This so-called off-label use is suggested by a similar mode of action or a similar pathology. The use of medicines beyond the marketing authorisation (off-label) or without marketing authorisation (unlicensed) implies that it is possible that there has been no adequate and in-standard consideration of its efficacy, safety and quality, or benefits-risks analysis for a different application or at least it is not available using the standard regulatory channels.<sup>2</sup> The drug Mediator for instance, was approved for treating diabetes but was also prescribed 'off-label' for weight loss. This indication was not included in the summary of product characteristics which caused fatal valvular heart diseases in hundreds of patients.

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<sup>1</sup> Strauss SA. 'Off-label' use of medicine: Some legal and ethical implications SA Practice Management 1998; 19(1): 12-19.

<sup>2</sup> The licensing scheme implemented does not only address the need to assess efficiency, safety and the quality of the product but also the standards and

procedures to carry out these evaluations and to ensure the actual application of those standards for the production of these products.



Yet, in practice off-label use is particularly common in the areas of oncology, obstetrics, and infectious disease (HIV/AIDS) and in the care of children, pregnant women or palliative care. Despite taking specific account of this reality by the public authorities – including through financial and administrative incentives intended to promote this research – in paediatrics,<sup>3</sup> off-label use and use of unlicensed drugs is still estimated to range from 10% to 55% of the prescriptions.<sup>4</sup> In oncology the use has been estimated at 50% or more.<sup>5</sup> There are no sound data, however, on the overall off-label use since there is mostly **no obligatory registration of the off-label prescription**. Moreover, as there is often no reimbursement by health insurance systems nor inclusion in covered health care packages, **off-label use can hardly be tracked** via reimbursement or coverage data unless the healthcare payer has implemented a control before or after the

reimbursement of the drug (e.g. chapter 4 National Institute for Health and Disability Insurance - NIHDI – also referred to as RIZIV/INAMI in Belgium).<sup>6</sup>

The reasons underlying off-label prescription can be various.<sup>7</sup> Off-label use is often a response to unmet medical needs. In some cases, off-label use is an alternative or the only remaining option if standard treatment(s) ha(s)(ve) failed. For some patients or patient groups (i.e. pregnant women, children, rare diseases...), there is often no alternative available. In this case, not prescribing the medicinal product off-label for which there are indications of efficacy could imply a risk for the patient's health. Apart from the medical cases where often no alternative is available, other drivers can influence the choice to opt for off-label prescription. A shortage of medicinal products with marketing authorisation, the practitioner's evaluation that authorised alternatives are less suitable in the case at hand or the cost of the authorised

<sup>3</sup> On February 28, 2002, the European Commission published a Consultation document named "Better Medicines for Children – Proposed regulatory actions in Paediatric medicinal products – which lead to adopting the Paediatric regulation 1901/2006. A central element in those measures was to refer to this need and provide with additional incentives to ensure a solution were off-label use of medicines for paediatrics would be limited.

According to the "Progress report on the paediatric regulation (EC) N°1901/2006" (COM (2013) 443), the Paediatric-use marketing authorisations (PUMA) concept (see 3.3.2.3) appeared to be disappointing. On the other hand, public funding of research appeared to be promising. [http://ec.europa.eu/health/files/paediatrics/2013\\_com443/paediatric\\_report-com\(2013\)443\\_en.pdf](http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf)

A study performed in a Finnish hospital evaluated the possible impact of the Regulation on the prevalence and the frequency on off-label use and use of unauthorized medicines. Prescribing for off-label use and unauthorized medicines was very common in the paediatric wards of the Kuopio University Hospital in 2001. The study was repeated in 2011 as it was conducted 10 years earlier. The prescribing for off-label use and unauthorized medicines was more prevalent in 2011 than in 2001 which indicates that the recent legislation has had only minor or no impact on the authorizing status of medicines commonly used in paediatric inpatients in specialized care.

It can be noted that the findings may become different now (2015), as the paediatric regime is now much more established.

Lindell-Osuagwu, L., M. Hakkarainen, et al. (2014). "Prescribing for off-label use and unauthorized medicines in three paediatric wards in Finland, the status before and after the European Union Paediatric Regulation." *J Clin Pharm Ther* 39(2): 144-53.

<sup>4</sup> Dell'Aera, M., A. R. Gasbarro, et al. (2007). "Unlicensed and off-label use of medicines at a neonatology clinic in Italy." *Pharm World Sci* 29(4): 361-7; Lindell-Osuagwu, L., M. J. Korhonen, et al. (2009). "Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature." *J Clin Pharm Ther* 34(3): 277-87. Santos, D. B., A. Clavenna, et al. (2008). "Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil." *Eur J Clin Pharmacol* 64(11): 1111-8.

<sup>5</sup> American Society of Clinical, O. (2006). "Reimbursement for cancer treatment: coverage of off-label drug indications." *J Clin Oncol* 24(19): 3206-8; Laetz, T. and G. Silberman (1991). "Reimbursement policies constrain the practice of oncology." *JAMA* 266(21): 2996-9; Poole, S. G. and M. J. Dooley (2004). "Off-label prescribing in oncology." *Support Care Cancer* 12(5): 302-5.

<sup>6</sup> <http://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/specialiteiten/hoofdstukken/Paginas/terugbetaling-specialiteiten-hoofdstukiv.aspx>

<sup>7</sup> S. Oberman, "Off-Label Use of Medicines – General Aspects, Challenges and Strategies", master thesis, 2013, p. 9



medicinal product being much higher than the off-label alternative may be important drivers. Physicians can also be encouraged to prescribe off-label because of the involvement of the industry in the education and promotion on off-label use, although pharmaceutical companies are legally not allowed to mention (without being asked) the off-label use to the medical profession. Both off-label use for medical need where no alternative exists and off-label use where an alternative on-label treatment is available fall within the scope of this report.

Although off-label prescription and use seem to be common practice, **different parties involved face uncertainties**. The competent authorities complain about this therapeutic use because there is most of the times no evidence of their safety and efficacy and/or because the risk-benefit has not been formally assessed. Information on off-label use is mostly limited to scarce information from case reports or expert opinions. Payers hesitate to reimburse this non-validated use. Prescribers feel uncomfortable, bearing the primary responsibility for determining when off-label prescribing is appropriate for patients. Sometimes the patient will be asked to sign an informed consent form, but as off-label use is often the sole (remaining) option or the more affordable one, patients will mostly be inclined to agree, even if the evidence on its efficacy and safety is scarce. Moreover, patients can experience problems with the continuity of the treatment. When the medicinal product is taken from the market (deflazacort, mexiletine) the off-label users lose their only treatment.<sup>8</sup> Yet, this is not inherent to off-label, also on-label users can face this situation.

**For pharmaceutical companies there may be a lack of legal and economic incentives to develop new indications or variations of existing indications.** The current legal infrastructure of medicine patents and regulatory exclusivity periods is designed to promote the development of new medicinal products, not new indications for existing products (see 3.3.2.1). Companies are therefore not inclined to request marketing authorisation for a new indication unless these new indications provide a competitive advantage, e.g. to get listed on hospital formularies. Furthermore, off-label prescribing is already widely practiced and recommended throughout the medical society. Sometimes very small markets, such as for orphan and paediatric indications are involved. As such, the cost of the usually long and laborious clinical development process required for demonstrating efficacy and safety of a new indication of an already approved medicine might simply not be worth the possible financial return. Moreover, additional study results include the risk that the drug is ineffective or presents safety problems, which can result in a decrease of sales. Another barrier may be the liability issues that may be linked to adverse events related to the pharmaceutical.<sup>9</sup>

Some argue that the regulatory structure incentivizes pharmaceutical companies to seek a narrow list of indications to enhance a rapid market entry and to reduce the investment in research.<sup>10</sup> Furthermore risk minimisation is targeted by precisely aligning the conditions of the drug approval with the inclusion and exclusion criteria in the phase III registration trials. Today, however, differentiation in diagnoses and treatment options are increasing and this dynamic process takes place at a much higher speed than the regulatory approval process. As such, there is a discrepancy between the actual medical "need" and the authorisation status of a product.

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<sup>8</sup> M. Dooms: Understanding off-label use and the new challenges. Orphanet Journal of Rare Diseases 2014 9(Suppl 1):O22.

<sup>9</sup> J. Woodstock et al., A shift in the regulatory approach, Drug information Journal, 1998, vol. 32, pp. 267-371

<sup>10</sup> S. Oberman, "Off-Label Use of Medicines – General Aspects, Challenges and Strategies", master thesis, 2013, p. 9





Despite the frequent off-label use in practice, there is too little documented evidence that this use has a positive safety-efficacy balance. The safety demonstrated for the on label use of a product does not (necessarily) cover a safe off-label use as factors as age of the patient, comorbidities, use of concomitant medication, drug interactions could be different in the off-label and on-label use.<sup>11</sup> As in principle,<sup>12</sup> solely the producer of the medicinal product is able to apply for registration of an indication or a modality of use, it remains possible not to try to evaluate the safety and efficacy of treatment and not to apply for registration. **From a scientific and social point of view, it may, however, be desirable to develop knowledge on an authorised product and to evaluate the safety and efficacy of that drug for indications or modalities of use that are not registered by the marketing authorisation holder.** To date, in absence of industry-financed research, a diverse group of other research sponsors (academia, government, non-profit organizations, and patient advocates) is already involved in conducting clinical trials.<sup>13</sup> **Registration of the indication or of the off-label modality, however, was to our knowledge never done by these research-sponsors.**

This report intends to formulate options for a framework for a better managed off-label use of medicines for Belgium. Although the study focuses on the Belgian situation, the possibility of a coordinating role at the European level is included in the study frame.

In a first chapter of the study, off-label use and the related relevant concepts are defined. The second chapter gives an overview of the existing legal framework related to the issue of off-label use on the European level. In a third chapter, the current legal framework in Belgium and in a selection of European as well as non-European countries is described. The fourth chapter analyses the policies in different countries in the light of the EU higher regulation. Based on the results of the analysis of the existing legal framework on the European level and the practices abroad, an overview of options for the management of off-label use for Belgium are drafted in the last chapter.

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<sup>11</sup> J. Mason et. Al., Off-label and unlicensed use and adverse drug reactions in children: a narrative review of the literature, *European Journal of Clinical Pharmacology*, Jan 2012, 68 (1): 21-28

<sup>12</sup> In theory, a third party can apply for a MA if solid dossier can be established. The access to the product, however, can be hampered by the producer. Moreover, according to article 126a of Directive 2001/83/EC, a Member State may for justified public health reasons authorise the placing on the market of that medicinal product, in the absence of a marketing authorisation or of a pending application for authorisation for a medicinal product, which has already been authorised in another Member State. [http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a\\_chap1\\_2013-06\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_2013-06_en.pdf)

<sup>13</sup> A diverse group of other research sponsors (academia, government, non-profit organizations, and patient advocates) is already involved in conducting

clinical trials today. The American Society of Clinical Oncology (ASCO), for instance plans to launch the first clinical trial in the Society's history in 2015. The study will offer patients with cancer access to molecularly targeted cancer drugs and collect real-world data on clinical outcomes to help oncologists learn the best uses of these drugs outside of approved indications. According to the ASCO Chief Medical Officer: "One of the major challenges to implementing personalized medicine is the lack of information about the risks and benefits of targeted drugs that are used off label to treat patients whose tumor harbors a genomic abnormality. "Other difficulties are lack of access to these agents for patients and interpretation by oncologists of the complex genomic test results. This ASCO-led clinical trial will address both challenges. <http://connection.asco.org/Magazine/Article/id/4163/New-ASCO-Study-Aims-to-Learn-from-Patient-Access-to-Targeted-Cancer-Drugs-Used-OffLabel.aspx>



## 1.2 Illustration of different types and modalities of off-label use

In the next section, we provide an overview of different types of off-label use examples to illustrate some of the difficulties and the inconveniences of the current system. At this time, the most well-known example of off-label use of a drug is probably the Avastin-Lucentis case, which will be elaborated in part 1.2.1. However, we would like to stress that the scope of this report on off-label use is much broader than this example.

### 1.2.1 Off-label use for cost considerations: The example of Avastin/lucentis

#### Background

Avastin (bevacizumab) and Lucentis (ranibizumab) are both monoclonal antibodies developed by Genentech. Lucentis is derived from the same parent monoclonal antibody as Avastin. Bevacizumab came on to the market first and is marketed for intravenous use in various cancers. It was widely prescribed off-label for intravitreal use of the eye disease 'wet age related macular degeneration' (AMD) before ranibizumab's approval by the National Institute for Health and Care Excellence in 2007.<sup>14</sup> Avastin is available for intravenous use in oncology in a 100mg/4ml vial or 400mg/16ml vial.<sup>15</sup> This formulation was not designed for intravitreal use and the volume is clearly a large multiple of the volume and dose needed to treat AMD. Intravitreal aliquots are typically compounded from these large vials.<sup>16</sup> The price per required dose of Avastin is way lower than for Lucentis. In Belgium, the cost for the health insurance is over €700 for an injection of Lucentis (the co-payment is very low) versus a non-reimbursed cost of about €40 per injection with Avastin.

<sup>14</sup> Cohen D. Why have UK doctors been deterred from prescribing Avastin? *BMJ*. 2015 Apr 1;350:h1654.

<sup>15</sup> Package leaflet: information for users Avastin 25 mg/ml concentration dissolution for infusion Bevacizumab. Via: [bijsluiters.fagg-afmps.be](http://bijsluiters.fagg-afmps.be).

<sup>16</sup> <http://eyewiki.ao.org/Bevacizumab>

<sup>17</sup> Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, et al. Ranibizumab and bevacizumab for treatment of

#### The evidence

Both in the US and UK, publicly funded trials comparing Avastin and Lucentis have been performed. In the US, funded by the National Eye Institute, the CATT trial comparing Avastin with Lucentis found that "*Ranibizumab (Lucentis) and bevacizumab (Avastin) had similar effects on visual acuity over a 2-year period. There were no differences between drugs in rates of death or arteriothrombotic events. The interpretation of the persistence of higher rates of serious adverse events with bevacizumab is uncertain because of the lack of specificity to conditions associated with inhibition of VEGF.*"<sup>17</sup> The higher rates of non-specific serious adverse events with Avastin was also difficult to interpret because people having more injections had lower adverse event rates.<sup>18</sup>

In the UK, funded by the National Institute for Health Research Health Technology Assessment programme, the interpretation of the two-year results of the IVAN trial was that "*ranibizumab and bevacizumab have similar efficacy. Reduction in the frequency of retreatment resulted in a small loss of efficacy irrespective of drug. Safety was worse when treatment was administered discontinuously. These findings highlight that the choice of anti-VEGF treatment strategy is less straightforward than previously thought.*"<sup>19</sup>

The authors of a systematic Cochrane review included data from nine studies (3665 participants), including six published (2745 participants) and three unpublished (920 participants) RCTs, none supported by industry. They concluded that "*non-industry sponsored RCTs could not determine a difference between intravitreal bevacizumab and ranibizumab for deaths, all serious systemic adverse events (SSAEs), or specific subsets of SSAEs in the first two years of treatment, with the exception of gastrointestinal disorders. The current evidence is imprecise and might vary across levels of*

neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012 Jul;119(7):1388-98.

<sup>18</sup> Cohen D. Attacks on publicly funded trials: what happens when industry does not want to know the answer. *BMJ*. 2015 Apr 1;350:h1701.

<sup>19</sup> Chakravarthy U, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet*. 2013 Oct 12;382(9900):1258-67.



patient risks, but overall suggests that if a difference exists, it is likely to be small. Health policies for the utilisation of ranibizumab instead of bevacizumab as a routine intervention for neovascular AMD for reasons of systemic safety are not sustained by evidence.”<sup>20</sup>

A recently published study in JAMA<sup>21</sup> tried to find out whether the distribution of bevacizumab through compounding pharmacies increases the risk for endophthalmitis, a potentially blinding eye infection, compared with the distribution of single-use vials of ranibizumab from the manufacturer. This retrospective cohort study used medical claims data from ambulatory care centers across the United States that were submitted to a large, national US insurer. The analysis involved 383 810 intravitreal injections given to 58 612 patients. The results of the study were as follows: “In total, 296 565 injections of bevacizumab were given to 51 116 patients and 87 245 injections of ranibizumab were given to 7496 patients. We found 71 cases of endophthalmitis (49 in the bevacizumab cohort and 22 in the ranibizumab cohort) for an endophthalmitis rate of 0.017% (95%CI, 0.012%-0.021%; 1 case per 6 061 injections) for bevacizumab and 0.025% (95%CI, 0.015%-0.036%; 1 case per 3 968 injections) for ranibizumab. After controlling for age, race, sex, injection-related diagnosis, and year of injection, we found no significant association with development of endophthalmitis after a bevacizumab injection compared with ranibizumab (odds ratio, 0.66 [95%CI, 0.39-1.09];  $P = 0.11$ ).” The authors conclude that this suggest that bevacizumab as currently used across the United States does not increase the risk for endophthalmitis.

### Licensing and reimbursement

Roche has acquired Genentech and holds the intellectual property rights for both drugs, although Novartis has the rights to market ranibizumab in Europe.<sup>18</sup> Despite repeated calls from politicians, Roche has never applied for a marketing authorisation for Avastin for ophthalmic conditions.<sup>14, 18</sup>

Nevertheless, in 2014, based on the above evidence, the French and Italian governments passed laws to allow the reimbursement of off-label medicines, specifically referring to bevacizumab.<sup>14</sup> The drug industry has filed a complaint with the European Commission against these decisions arguing this undermines the EU regulatory system, patent protections, and incentives for drug development.<sup>14</sup>

*“In its anti-cancer drug, bevacizumab, drug developer Genentech has created what may be the world’s first “not me” (as opposed to “me too”) drug ... Despite evidence that it works in macular degeneration, the manufacturers and marketers are actively discouraging its use for this condition, even going so far as taking legal action to prevent such off-label use. Why? Because they want people to use their other drug, ranibuzimab, which is licensed for treating macular degeneration. ... The bottom line is that ranibuzimab is about 12 times more expensive”*<sup>22</sup> In Belgium, the cost for the health insurance is over €700 for an injection of Lucentis (the co-payment is very low) versus a non-reimbursed cost of about €40 per injection with Avastin, offering a huge opportunity for more efficient use of public money.<sup>23</sup>

### The story goes on...

At the moment of writing the report, several national authorities have reacted to the situation. On 27 February 2014, the Italian National Competent Authority (NCA) adopted a decision condemning arrangements by Roche and Novartis to curb off-label use of Avastin for the treatment of wet AMD. Roche and Novartis were fined €180 million (\$221.6 million) for manipulating sales of their eye medication. The findings of that decision, and the practices in question, are factually and legally closely related to the Italian regulatory framework, which authorises the off-label use of certain pharmaceuticals under specific conditions.

<sup>20</sup> Moja L, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2014 Sep 15;9:CD011230.

<sup>21</sup> Brian L. VanderBeek, MD, MPH; Sarah G. Bonaffini, BS; Liyuan Ma, MS Association of Compounded Bevacizumab With Postinjection

Endophthalmitis JAMA Ophthalmol. Published online August 13, 2015. doi:10.1001/jamaophthalmol.2015.2556

<sup>22</sup> Godlee F. Avastin versus Lucentis. BMJ 2012;344:e3162.

<sup>23</sup> <http://sanconet.be/nieuws/200-miljoen-euro-besparingen-gemist-in-de-gezondheidszorg-lucentis-vs-avastin>

Accordingly, France passed a decree allowing for reimbursement of off-label medicines for economic motives, and specifically mentioned Avastin. A temporary recommendation for use (RTU – Recommendation Temporaire d'Utilisation) of Avastin for the treatment of wet AMD was established.<sup>24</sup> Roche opposed to this decision since other authorized therapeutic alternatives are available.<sup>25</sup> Nevertheless, the ANSM provided a positive advice for the RTU that came into force on 1 September 2015 for a period of three years and can be extended after a re-evaluation of available evidence.<sup>24</sup>

In the Netherlands, already in 2012, CVZ (College Voor Zorgverzekering, currently ZINL - Zorginstituut Nederland) recommended to remove the drug ranibizumab (Lucentis®) by 1 January 2015 from the insured package for AMD, unless convincing evidence could be delivered that shows that the product has a therapeutic value compared with a comparative treatment in patients who respond inadequately to bevacizumab (Avastin®) and/or have a hypersensitivity for the product or suffer side effects requiring discontinuation of this therapy.<sup>26</sup> This advice was a.o. based on the BRAMD-study (Bevacizumab Ranibizumab Age-related Macular Degeneration), sponsored by the Dutch government (ZonMw), comparing both drugs. ZINL advised to reimburse the cheaper alternative and also the Dutch guidelines included Avastin in first line, saving more than €60 million per year.

Currently (30 July, 2015), Avastin is included in the DBC (diagnose behandeling combinatie) and Lucentis is categorized as an expensive drugs (€956.29 per vial, [www.medicijnkosten.nl](http://www.medicijnkosten.nl)) which can be declared as add-on, just like Eylea, Remicade, Macugen, Verteporfin and Humira (personal communication). The Dutch practice guidelines published in 2014 recommend Avastin as the first choice for the treatment of AMD, on the basis of cost differences, non-inferiority versus other treatments and current

knowledge about systemic side effects.<sup>27</sup> According to a Dutch expert, the cheaper drug Avastin would be used in about 80-90% of all cases (personal communication).

In the UK, NICE is currently producing a clinical guideline on diagnosis and management of macular degeneration. Bevacizumab is referred to in the draft scope of the guideline: *“Although bevacizumab is in use in the UK and elsewhere for the treatment of wet AMD, the Medicines and Healthcare Products Regulatory Agency regards it as unlicensed for this indication because its use requires it to be reconstituted. Licensed alternatives (such as aflibercept, pegaptanib sodium, ranibizumab and verteporfin) are available. Although there is evidence (including research funded by the National Institute for Health Research) demonstrating the safety and efficacy of bevacizumab for treating AMD, which will be referred to in the guideline, our ability to refer to its use in routine clinical practice for this condition is constrained by its licensing status. Therefore, while bevacizumab will be included in the evaluations carried out to develop the guideline, and information on its properties and use may be included in the final guideline, no recommendation for its use will be made in any case where a licensed alternative is available”*<sup>28</sup> Although NICE does not normally appraise drugs outside of their licensed indications, it can happen at request of the Department of Health when they decide to refer bevacizumab to NICE for consideration as part of its technology appraisal programme.

NHS organisations in England are legally required to fund the recommendations in NICE technology appraisal guidance. However, it is important to note that drugs do not have to be appraised by NICE in order that they can be available on the NHS. NICE is only asked to appraise a very small percentage of the drugs that are available. In the absence of NICE guidance decisions on whether to fund, other treatments in the Drugs Tariff

<sup>24</sup> [http://ansm.sante.fr/content/download/78441/994175/version/1/file/RTU\\_Avastin-DMLA\\_Decision\\_24-06-2015.pdf](http://ansm.sante.fr/content/download/78441/994175/version/1/file/RTU_Avastin-DMLA_Decision_24-06-2015.pdf)

<sup>25</sup> <http://www.rocche.fr/medias/actualites/rocche-reitere-son-opposition-a-une-rtu-d-avastin-dans-la-dmla.html>

<sup>26</sup> <https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/rapporten-en-standpunten/2012/1208-advies-ranibizumab-lucentis-bij-de-indicatie-%E2%80%98neovasculaire-leeftijdsgebonden-maculadegeneratie%E2%80%99/1208-advies->

[ranibizumab-lucentis-bij-de-indicatie-%E2%80%98neovasculaire-leeftijdsgebonden-maculadegeneratie%E2%80%99/Advies+ranibizumab+%28Lucentis%29+bij+de+indicatie+%E2%80%98neovasculaire+leeftijdsgebonden+maculadegeneratie%E2%80%99.pdf](http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0658/documents/ranibizumab-lucentis-bij-de-indicatie-%E2%80%98neovasculaire-leeftijdsgebonden-maculadegeneratie%E2%80%99/Advies+ranibizumab+%28Lucentis%29+bij+de+indicatie+%E2%80%98neovasculaire+leeftijdsgebonden+maculadegeneratie%E2%80%99.pdf)

<sup>27</sup> [http://richtlijnendatabase.nl/richtlijn/leeftijdsgebonden\\_maculadegeneratie/lmd\\_behandeling\\_en\\_follow-up/lmd\\_eerste\\_keus\\_anti-vegf.html#uitgangsvraag](http://richtlijnendatabase.nl/richtlijn/leeftijdsgebonden_maculadegeneratie/lmd_behandeling_en_follow-up/lmd_eerste_keus_anti-vegf.html#uitgangsvraag)

<sup>28</sup> <http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0658/documents>





are taken by local NHS bodies. NICE does not have any involvement in the inclusion of technologies in the Drugs Tariff. Local commissioners can negotiate local deals and prices directly with manufacturers (personal communication with NICE).

The World Health Organization (WHO) rejected to include the licensed drug Lucentis to be added on the list of essential medicines, while the off-label use of Avastin for ophthalmic use is supported by including it on this list.<sup>29 30</sup>

In Belgium, FAGRON Compounding Services (be.fagron.com) prepares the off-label eye injections under aseptic conditions. Data from this firm are further analysed to support policy decisions on the use of off-label Avastin for AMD.

At the end of November 2014, Test-Achats/Test Aankoop (a Belgian consumer organization), alongside consumer groups from Spain, Portugal and France, lodged a complaint against Roche and Novartis, the producer and distributor of Avastin and Lucentis.<sup>31</sup> The consumer groups concerned allege that the two pharmaceutical companies have come to an agreement to prevent the use of the cheaper drug Avastin, so as to maximise the profits they receive. The Commission stated that it is aware of Test-Achats' complaint to the Belgian National Competition Authority (NCA) alleging the existence of an anti-competitive agreement.<sup>32</sup> In order for this alleged conduct to infringe European antitrust rules, it would need to meet the requirements of Article 101 of the Treaty on the Functioning of the European Union, which in essence prohibits "agreements between undertakings [...] which have as their object or effect the prevention, restriction or distortion of

competition within the internal market". The Commission stated that it is aware that this situation has raised concerns in several Member States. It is gathering more information and remains in close contact with NCAs, notably with the French NCA, which has conducted inspections at the premises of some of the companies involved.

### 1.2.2 Off-label use of orphan drugs

Benefits are granted to pharmaceutical companies seeking the approval of "orphan drugs", for rare diseases (see 3.3.2).<sup>33</sup> Sometimes these drugs are also used in an off-label indication (Litak used as Leustatin for non-Hodgkin Lymphoma, Revatio used as Viagra for other indications,<sup>34</sup> Thalidomide, used for palliative care (cachexia)). There is a large concentration of approved orphan drugs in oncology.<sup>35</sup> A possible explanation is that drugs used to treat cancer are, by far, the most profitable. Moreover, this profitability could be explained, at least in part, by the frequent off-label use of these drugs.<sup>36</sup> Whereas the mechanism of the economic incentives only apply to rare disease, pharmaceutical companies will thus be able to make profit from the off-label use as well. Basically, the problem here is that the approval of a new indication can exclusively be sought by the pharmaceutical company that produces the drug. In Belgium, it can be presumed that the off-label use of orphan drugs is rather limited.<sup>37</sup> The high price of an off-label used orphan drug will have to be borne by patients, unless they can benefit from the "medical need" program (cfr. infra) or if the

<sup>29</sup> [http://www.who.int/medicines/publications/essentialmedicines/EML2015\\_8-May-15.pdf](http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf)

<sup>30</sup> <http://www.theguardian.com/society/2015/may/17/cheap-blindness-drug-should-be-made-widely-available-says-who>

<sup>31</sup> <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+WQ+P-2015-000937+0+DOC+XML+V0//FR&language=FR>

<sup>32</sup> <http://www.europarl.europa.eu/sides/getAllAnswers.do?reference=P-2015-000937&language=FR>

<sup>33</sup> Denis A, Simoens S, Fostier C, Mergaert L, Cleemput I. Policies for Rare diseases and Orphan Drugs. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2009. KCE reports 112C (D/2009/10.273/32)

<sup>34</sup> Viagra was first on the market and was off-label used for pulmonary hypertension. The firm remarked (repurposed) the drug with a slightly different dose as "Revatio"

<sup>35</sup> de Varax AM, Letellier M, Börtlein G, ALCIMED. Study on Orphan Drugs: Phase I—Overview of the Conditions for Marketing Orphan Drugs in Europe. Paris, France: ALCIMED, 2005; Register of designated Orphan Medicinal Products, <http://ec.europa.eu/health/documents/community-register/html/orphreg.htm>

<sup>36</sup> Coté A. and Keating B. What is wrong with orphan drug policies? Value in Health. Volume 15, Issue 8, December 2012, Pages 1185–1191

<sup>37</sup> Personal Communication Marc Dooms



reimbursement conditions of the Special Solidarity Fund (SSF) are fulfilled.<sup>38</sup> Reimbursement by the SSF is often linked, however, to specific conditions (i.e. certificate delivered by oncologist, haematologist...) that are often difficult to fulfil if a drug is off-label used for another indication.

### 1.2.3 Drug repurposing or rediscovering

Drug repurposing (also known as drug repositioning or drug re-profiling) is the application of known drugs and compounds to new indications.<sup>39</sup> This is an alternative strategy in drug development with a history of successful repositioning of existing drugs, in oncological as well as in non-oncological contexts. The most well-known example is the drug sildenafil (Viagra), originally developed by Pfizer as a treatment for hypertension and angina, which was then repurposed as a successful treatment for erectile dysfunction.<sup>40</sup> One of the most dramatic examples of the "known compound-new target" approach is the revitalization of Thalidomide, prescribed in the 1950s for nausea and insomnia in pregnant women, which was found to cause severe birth defects in children whose mothers took the drug in the first trimester of pregnancy. Scientists later discovered that in addition to its sedation effect, thalidomide had antiangiogenic and immunomodulatory effects, including the inhibition of TNF alpha.

In contrast with the "classical" off-label use, which stems from rather accidental opportunities to re-use an existing drug, drug repurposing is targeted, systematised and rational. For pharmaceutical companies it is an attractive strategy for drug development because of the lower cost of R&D (research & development) and a lower cost of market access. Drug repurposing is also an attractive drug development strategy for orphan diseases. Given the time consuming development trajectory and the high

costs of drug development, pharmaceutical and biotechnology companies usually focus on potential therapies with the highest likelihood of generating a good financial return. Moreover, conventional approaches to drug development are often not feasible for rare diseases, which offer not only small markets but also small populations for participation in clinical trials. This often implies that potential therapies for rare diseases, including for life-threatening conditions, often don't get to the stage of early development.

In the US, a new resource has been established by the US FDA's Office of Orphan Products: Rare Disease Repurposing Database (RDRD) for drug developers.<sup>41</sup> It is a compilation of drugs that have shown promise for treating orphan diseases and already have FDA approval or designation. It is a database of products that have received orphan status designation (i.e. they have been found 'promising' for treating a rare disease) and are already market approved for the treatment of some other diseases. Since these compounds already have FDA approval, repositioning these drugs for a new orphan drugs indication could in certain cases be relatively quicker and less expensive for the developer, and could therefore help patients by getting to market quicker.

Life-cycle management strategies often result in the extension of the value of a pharmaceutical brand. Some pharmaceutical companies bring the old substance on the market with a higher price. Simoens et al. argue that some of the Belgian hospital prices of drugs repurposed for orphan diseases are not justified.<sup>42</sup> They found that medicine prices for the rare indication were nearly always higher than for the common indication – and in some cases this amounted to a multiplication with factor 200 (e.g. Histamine). In the cases they examined, evidence supporting the effectiveness of the medicine for the rare indication had often been published many years prior to the

<sup>38</sup> <http://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/bijzonder-solidariteitsfonds/Paginas/default.aspx>; art. 25 to 25 decies Law related to the compulsory health and disability insurance coordinated on the 14th of July 1994, *B.S./M.B.* 27 August 1994

<sup>39</sup> Sleigh SH, Barton CL (2010). "Repurposing Strategies for Therapeutics". *Pharm Med* 24 (3): 151–159

<sup>40</sup> Pantziarka P, Bouche G., Meheus L., Sukhatme V., Vikas P. and Sukhatme P. The Repurposing Drugs in Oncology (ReDO) Project. *Ecancermedalscience*. 2014; 8: 442.

<sup>41</sup> <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm>

<sup>42</sup> Simoens S, Cassiman D, Picavet E, Dooms M: Are some orphan drugs for rare diseases too expensive? A study of purchase versus compounding costs. *Drugs Ther Perspect* 2011, 27(10):24-26



orphan drug designation application. Given the available effectiveness evidence, the possibly reduced costs of R&D and market access, a change in pharmaceutical form may justify a price increase but not to this extent. High prices add to the budget impact of treating rare diseases and may hamper patients' access to therapy. Therefore the authors argued that there is a need to individually assess repurposed drugs.

The focus on profit generation in the repurposing of pharmaceuticals may also have an impact on the business strategy to keep the product on the market for the existing indication. In September 2012, Genzyme removed the Campath brand of alemtuzumab, a leukaemia drug, from commercial availability in about 50 markets, including the United States and the European Union.<sup>43</sup> The withdrawal was triggered by the fact that Genzyme did not want Campath to be used off-label in the multiple sclerosis setting awaiting the approval for a lower-dose formulation of alemtuzumab for a new indication, i.e. multiple sclerosis. Although sacrificing one patient community in favour of a more lucrative one, the firm decided to make Campath available free of charge under a patient-access program.

In many cases repurposed drugs are generic or end of patent life-time products. Once pharmaceutical companies lose the patent (and thus monopoly-) protection and generics enter, patients can use the low-cost generics regardless of whether they are taking the drug for an old or new indication. As such, financial incentives to invest in trials for new uses of old drugs will often be lacking. Yet, without the evidence from clinical trials, the potential economic and medical benefits that will accrue from the adoption of these low-cost repurposed drugs will not be realised. In absence of involvement of the pharmaceutical industry, other stakeholders, such as academia, not-for-profit organisations, government-funded bodies, should fund these clinical trials. The Belgian not-for-profit organisation the Anticancer Fund, for instance, is already involved in funding a number of such trials.<sup>44</sup>

#### 1.2.4 Off-label use of targeted therapies

Significant advances in sequencing techniques and molecular diagnostics do accelerate the field of targeted therapies. Using *Next Generation Sequencing* (NGS) it is possible to sequence a panel of genes in a single run. This way mutations in multiple cancer cell genes can be identified and the targeted drug selected. This approach is currently mainly used for clinical research purposes. Cancer patients in larger centres are more and more tested to evaluate their possible inclusion into clinical trials with new targeted drugs. The necessary equipment and reagents have become affordable, allowing also smaller centres to invest in this technology. Oncologists may want to use the test results and experiment with off-label targeted drugs. Sometimes this happens outside of a clinical research framework, without the necessary supporting clinical evidence. The question rises how restrictive the healthcare payer should be with such off-label use of such expensive targeted drugs? Moreover, the reliability of the results of the new tests in the routine practice in smaller centres can also be questioned.

More and more medicines come to the market, targeted to a specific molecular pathway that can be identified before treatment starts. Usually, a companion diagnostic is used to make sure the disease of the patient is characterised by this particular pathway, which can then be targeted. Precision medicine (also named targeted treatment or personalised medicine or stratified medicine) has been defined as identifying the right drug, for the right patient, at the right dose, at the right time. The advantage of this targeted approach is that the patients treated are more likely to respond to the treatment, and that one avoids that patients who are unlikely to respond are exposed to a potentially toxic treatment. Next generation sequencing is currently mainly used in a clinical research setting. This can be in trials with new targeted drugs or in rescue treatment trials in heavily pre-treated patients where the identified mutations guide the off-label use of existing targeted drugs. This may lead to an extension of indications of the existing targeted drug. However, an increase in the off-label use is more likely to be seen. Indeed this phenomenon of increased use of targeted

<sup>43</sup> <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM374186.pdf>

<sup>44</sup> P. Pantziarka, G. Bouche, L. Meheus, V. Sukhatme, P. Vikas, P. Sukhatme and P. Vikas. The Repurposing Drugs in Oncology (ReDO) Project. *Ecancermedicalscience*. 2014; 8: 442.



drugs off-label has already been observed in routine care in case the NGS panel test identifies a mutation in a gene that would otherwise not have been interrogated. Any potential health effects or the possible budget impact of increased off-label use of targeted drugs are however not well documented today.<sup>45</sup>

### 1.2.5 Shorter treatment duration which might be as effective as approved treatment schedule: the example of Herceptin

In 2006, KCE published a report on the use of Herceptin (trastuzumab) for the treatment of early HER2 positive breast cancer. Herceptin is registered in this indication with a treatment schedule of one year based on the HERA (Herceptin Adjuvant) trial. However, at the moment the KCE report was performed, two trials were already available indicating the potential of a short-treatment regimen. Firstly, there was the relatively small government sponsored FinHer trial<sup>46</sup> in which the drug was only administered for 9 weeks in a pre-anthracycline regimen. The disease-free survival of this study in comparison with the other available studies at that time showed the potential of this regimen: the hazard ratio for disease-free survival was 0.42 (0.21-0.83) in the FinHer trial whereas this was 0.54 (0.43-0.67) in the HERA trial.<sup>47</sup> Secondly, the E2198 phase 2 study compared 10 weeks with 12 months of trastuzumab treatment. This trial was not designed to test efficacy and not powered to determine equivalence. However, the 5-year overall survival was 88% in the 10-week treatment schedule versus 83% for the one-year treatment (p=0.29).<sup>48</sup> Two HTA institutes mentioned that these results supported the efficacy of short duration concurrent trastuzumab

therapy when administered before anthracycline containing chemotherapy, as demonstrated in the FinHer study.<sup>47, 49</sup> At that moment, only indirect comparisons between the shorter and longer treatment schedule indicate the potential of the shorter treatment regimen. One of the recommendations of the KCE report was the following: "A clinical trial comparing 9 weeks of trastuzumab pre-anthracycline with the 52-week post-chemotherapy regimen should be started without delay."<sup>47</sup>

Also the UK researchers were confronted with the same issue. According to these researchers, one of the key issues is that "a small study (the FinHer trial,<sup>46</sup> n=229), excluded from the manufacturer's submission, raises the possibility of an equally effective but shorter regimen, incurring lower cost and toxicity but with greater patient convenience."<sup>49</sup> This was unfortunately not explicitly taken into account in their economic modelling. In a comment in the Lancet, the same authors explain this and mention the following: "New Zealand's drug-governing body, PHARMAC, is the first to suggest that the uncertainty surrounding the HERA schedule remains too great to justify the expenditure, and has commissioned a feasibility study to evaluate whether it should fund the FinHer regimen.<sup>50</sup> NICE could not ask us to evaluate the FinHer schedule because its remit is restricted to licensed indications and Roche sought marketing authorisation for a 1-year schedule only. We could speculate that Roche has little desire to develop a regimen that would reduce the use of trastuzumab significantly. Instead, by contrast, HERA is investigating whether more, rather than less, treatment is beneficial. In England and Wales, a schedule that might be as good and "may facilitate

<sup>45</sup> Van den Bulcke M, San Miguel L, Salgado R, De Quecker E, De Schutter H, Waeytens A, Van Den Berghe P, Tejpar S, Van Houdt J, Van Laere S, Maes B, Hulstaert F. Next generation sequencing gene panels for targeted therapy in oncology and haemato-oncology. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 240. D/2015/10.273/26.

<sup>46</sup> Joensuu H, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. The New England journal of medicine. 2006 Feb 23;354(8):809-20.

<sup>47</sup> Huybrechts M, et al. Trastuzumab in Early Stage Breast Cancer. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE). KCE report 34. 2006.

<sup>48</sup> Sledge G, et al. Pilot trial of paclitaxel-Herceptin adjuvant therapy for early stage breast cancer (E2198). Breast Cancer Res Treat. 2001(69):209. Abstract 4.

<sup>49</sup> Ward S, et al. Trastuzumab for the Treatment of Primary Breast Cancer in HER2 Positive Women: A Single Technology Appraisal; May 2006.

<sup>50</sup> PHARMAC. Herceptin status unchanged following further PTAC advice; Oct 16, 2006.





*lower cost, greater patient convenience, and reduced risk of cardiotoxicity*<sup>51</sup> is not considered further.<sup>52</sup>

### 1.3 Research questions

The above mentioned examples reveal that, basically, problems in off-label use can be situated at two levels. A medicine can be used off-label because the **pharmaceutical company omits to take steps to extend the approval, although (indications of) evidence of efficacy and safety is available**. This practice can take place with or without the availability of an existing alternative<sup>53</sup>. If the pharmaceutical company does not have enough interest to pursue the approval on a specific indication, this will be left unauthorised, and the (evidence-based) use of the drug will be off-label. Off-label use can also fall into the so-called 'grey zone' of evidence-based medicine, within which **high-level evidence is difficult to reach even for treatments which are likely effective**. This may be the case for rare diseases, or in paediatrics which do not lend themselves to large clinical studies. In this case, a balance should be found between offering new drugs to the patients as early as possible while controlling the risk–benefit ratio. Based on the foregoing, the following research questions will be studied in the report:

#### 1.3.1 First research question

**What powers do national authorities have under EU law to manage off-label use and under what conditions?**

#### 1.3.2 Second research question

**Can off-label use be brought in-label through a new marketing authorisation or a variation to the existing marketing authorisation(s)?**

#### 1.3.3 Third research question

**How can relevant evidence be gathered on off-label use of medicines?**

<sup>51</sup> SABCS. Trastuzumab in combination therapy for HER2-positive early breast cancer patients. San Antonio Breast Cancer Symposium Newsletter. 2005(2):2-3.

<sup>52</sup> Hind D, et al. Questions about adjuvant trastuzumab still remain. Lancet. 2007 Jan 6;369(9555):3-5.

## 1.4 Methodology

In order to evaluate the hypotheses of using drugs off-label in various modalities as described in 1.3, this study reviewed the existing legal framework on the European level. Additionally, the current legal framework in Belgium and in a selection of European as well as non-European countries was studied. Furthermore, the application of the relevant national regulations in case-law and the compatibility with the jurisprudence of the European Court of Justice was checked. Based on the results of the analysis of the existing legal framework on the European level and the practices abroad, an overview of options for the management of off-label use for Belgium were presented.

The following information sources were consulted in the conduct of this study:

- Belgian and European legal databases (BELGIQUELEX, EURLEX)
- Communications, Guidelines and reports of the European Commission, Parliament and Council
- Parliamentary work of the European and national legislation
- Position papers from professional and sectorial associations
- Articles published in scientific or legal publications
- Legal experts and lawyers from across Europe were consulted
- Official websites and documentation from national health products and reimbursement authorities in various European countries
- Experts in the field and representatives of relevant institutions and associations were consulted. Names of experts and their affiliations are listed in the Colophon of the report.

<sup>53</sup> Where referring to "alternatives", we consider a specific pharmaceutical product, registered for the same indication, regardless of quality or other preference.



## 2 DEFINITIONS

### 2.1 Marketing authorisation

**Before any new medicine can be sold on the European market, it must receive a marketing authorisation (MA).** The European system for the “authorisation” of medicinal products for human and animal use was introduced with the objective of ensuring that safe, effective and high quality medicines could quickly be made available to citizens across the European Union. The European system offers **several routes for the authorisation of medicinal products**.<sup>54</sup>

- The **centralised procedure**, created by Regulation (EEC) No 2309/93, later replaced by Regulation 726/2004/EC on the authorisation and supervision of medicinal products and establishing a European Medicines Agency (EMA)<sup>55</sup> (Regulation 726/2004/EC) allows applicants to obtain a MA that is valid throughout the EU after a single application and evaluation.

It is compulsory for some specific products, including products derived from biotechnology, for orphan medicinal products and for medicinal products for human use which contain an active substance authorised in the EU after 20 November 2005 (the entry into effect of Regulation 726/2004/EC) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes.

Applications for the centralised procedure are made directly to the European Medicines Agency and lead to the granting of a European marketing authorisation by the Commission which is binding in all Member States.

- Each EU Member State (MS) has its own **national authorisation procedure** for the authorisation, within their own territory, of medicines that fall outside the scope of the centralised procedure. There are two

possible routes available to companies aiming at obtaining harmonised national authorisations for these medicines:

- The **mutual recognition procedure**, which is set out in Directive 2001/83/EC on the Community code relating to medicinal products for human use<sup>56</sup> (Directive 2001/83/EC), aims at obtaining a MA in one or several Member States, when the medicinal product has already been granted a MA by at least one country in the European Community. In this case, the applicant requests one or more “concerned member states” (CMS(s)) to mutually recognize the authorization granted by the “reference member state” (RMS). If the application is successful, the original marketing authorisation issued by RMS is adopted into identical authorisations by the CMS.
- The **decentralised procedure**, which is set out in Directive 2001/83/EC as well, is also based on recognition by national authorities of a first assessment performed by one MS. The difference lies in that it applies to medicinal products which have not received a MA at the time of application. Through this procedure an application for the MA of a medicinal product is submitted simultaneously in several MS, one of them being chosen as the RMS. At the end of the procedure national marketing authorisations are granted in the RMS and in the CMS.

The MA procedure includes an assessment of a dossier, in which the future marketing authorisation holder (MAH) provides evidence for the safety, efficacy, and quality of the product.<sup>57</sup> The summary of product characteristics (SmPC) sets out the agreed position of the medicinal product as distilled during the course of the assessment process, including the registered and authorised indications for the named product. It further includes the qualitative and quantitative composition, pharmaceutical form, therapeutic indications, posology, method of administration, contraindications and special warnings and precautions for use. It serves as

<sup>54</sup> European Commission, DG Health & Consumers, *Authorisation Procedures for medicinal products*, [http://ec.europa.eu/health/authorisation-procedures\\_en.htm](http://ec.europa.eu/health/authorisation-procedures_en.htm)

<sup>55</sup> OJ L 136, 30.04.2004, p. 1.

<sup>56</sup> OJ L 311, 28.11.2001, p. 67.

<sup>57</sup> The licensing scheme implemented does not only address the need to assess efficiency, safety and the quality of the product but also the standards and procedures to carry out these evaluations and to ensure the actual application of those standards for the production of these products.



the basis of information about the medicinal product for doctors and healthcare professionals.<sup>58</sup> According to the General Court of the European Union, “*It is apparent from the Guideline<sup>59</sup> that the role of the summary of product characteristics is to define the medicinal product as approved, that is to say, for the approved therapeutic indications, and that it must contain information on the relevant studies which support the therapeutic indication. In addition, it states that the summary must contain information that is relevant to the prescribing physician. Accordingly, statements relating to the efficacy of the medicinal product concerned for therapeutic indications other than those approved does not form part of the information required by the Guideline.*”<sup>60</sup>

The marketing of medicinal products is highly regulated at the EU level. According to the recital 2 in the preamble to Directive 2001/83/EC, “[t]he **essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health**”. However, as stated in recital 3 in the same preamble “*this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community*”. On the other hand, MSs play a significant role in the protection of the public health. In accordance with the second to fourth recitals of Directive 89/105/EEC relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems<sup>61</sup> (Directive 89/105/EEC), **every MS can control the**

**prices of medicinal products sold on its territory with the aim of ensuring the viability of its health insurance system.** Furthermore, MSs may also want broader protection for public health. There must be measures available that ensure a continued and appropriate supply across the territory of each MS, which will allow it to meet the demand of all its residents.

## 2.2 Off-label use

Directive 2001/83/EC does not define the term off-label use. However, in Annex I to its Guideline on good pharmacovigilance practices, EMA specifies that **off-label use relates to “situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information”**.<sup>62</sup> Further, Article 1, 16° of Directive 2001/82/EC on the Community code relating to veterinary medicinal products<sup>63</sup> defines off-label use as “[t]he use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics, including the misuse and serious abuse of the product”.

In practice, the term off-label use refers to the prescribing or administration of an authorized medicinal product outside any of the terms of the marketing authorisation, as reflected in the SmPC. This might include use for a different indication, at a different dosage (or dosage frequency), duration of use, different method of administration, or use by a different patient group (for example, children or pregnant women).<sup>64</sup> One or more of these items will be reference to in the report as (off-label) ‘modality’.

<sup>58</sup> State Institute for Drug Control, “Marketing authorisation of pharmaceuticals”, [www.sukl.eu/medicines/marketing-authorisation-of-pharmaceuticals](http://www.sukl.eu/medicines/marketing-authorisation-of-pharmaceuticals); DG Enterprise and industry, “A guideline on summary of product characteristics (SmPC)”, September 2009, p. 2, [http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc\\_guideline\\_rev2\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf)

<sup>59</sup> Guideline on Summary of Product Characteristics adopted by the Commission in September 2009; [http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc\\_guideline\\_rev2\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf)

<sup>60</sup> Case T-452/14, Laboratoires CTRS, recital 115.

<sup>61</sup> OJ L 40, 11.02.1989, p 8.

<sup>62</sup> EMA, Guideline on good pharmacovigilance practices, EMA/876333/2011 Rev. 3 of 28 April 2014,

[www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/05/WC500143294.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf).

<sup>63</sup> OJ L 311, 28.11.2001, p. 1.

<sup>64</sup> A. Neubert, I. Wonga, A. Bonifazi et al., “Defining off-label and unlicensed use of medicines for children: Results of a Delphi survey”. *Pharmacological Research* 2008; P. Bogaert and A. Schwabl, “Cost considerations should not drive off-label drug use in the EU”, *Scrip Regulatory Affairs*, June 2012, 7; EMA, Guideline on good pharmacovigilance practices, EMA/876333/2011 Rev. 3 of 28 April 2014, [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/05/WC500143294.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf).



### 2.3 Use of unauthorized medicinal products

Off-label use should be distinguished from the use of **unauthorised medicinal products** which are products that **do not have a valid marketing authorisation** in the EU member state where they are being used.

**The use of unauthorised medicinal products** is in principle prohibited but there are some exceptions: based on the underlying concern for patient safety, EU law foresees limited possibilities for the use of non-authorized medicinal products:

- In **authorised clinical trials**, as set out in Directive 2001/20/EC on the conduct of clinical trials (Directive 2001/20/EC).<sup>65</sup>

A Clinical trial is defined as *“any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.”* This definition includes testing of products already with a MA in a way different from the authorized form or for an unauthorized indication (Article 2(a) of Directive 2001/20/EC).

- In case of **pharmacy-made preparations**, as set out in national legislation.

Article 3 of Directive 2001/83/EC states that this Directive shall not apply to:

- *“Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula)”*.
- *“Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula)”*.
- Under one of the other exceptions in Directive 2001/83/EC and Regulation 726/2004/EC namely: **special needs, emergency situations** and **compassionate use**.
  - **Special needs** (Article 5(1) of Directive 2001/83/EC): this concept refers to fulfilling special needs, by excluding medicinal products supplied in response to a *bona fide* unsolicited order,<sup>66</sup> formulated in accordance with the specifications of an authorized healthcare professional and for use by an individual patient under his direct personal responsibility from the provisions of Directive 2001/83/EC (Article 6quater, §1, 1°) Law on medicinal products of 25 March 1964). *“This exception implements the principle of therapeutic freedom for prescribing physicians. As such, it is an exception to the general rule and as such is strictly limited to individual, discretionary decisions of physicians where the doctor takes personal responsibility for prescribing the medicine to the patient after having individually examined him or her and thereafter follows closely how that patient reacts to the medicine.”*<sup>67</sup>

<sup>65</sup> OJ L 121, 01.05.2001, p. 34.

<sup>66</sup> A 'bona fide unsolicited order' means that the medicinal product must have been prescribed by the doctor as a result of an actual examination of his patients and on the basis of purely therapeutic considerations.

<sup>67</sup> J. Killick and M. Kritikos, “The GMC Decides Not To Relax Its Guidelines to Permit Broader Prescribing of Off-Label and Unlicensed Medicines, Including



- **Emergency situations** (Art. 5(2) and (3) of Directive 2001/83/EC): Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm. In case, member States need to lay down provisions in order to ensure that marketing authorisation holders, manufacturers and health professionals are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product otherwise than for the authorised indications or from the use of an unauthorised medicinal product, when such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.
- **Programs of compassionate use** (Article 83 of Regulation 726/2004/EC): this concept refers to making a medicinal product available, for compassionate reasons, that can qualify for the centralized procedure to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a MA or must be undergoing clinical trials (Article 6<sup>quater</sup>, §1, 2° Law on medicinal products of the 25 March 1964 and Article 106 Royal Decree of 14 December 2006 relating to medicines for human and veterinary use).

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*”.<sup>68</sup>

**Compassionate use programs need to be distinguished from Medical Need Programs (see also 6.1.1).** The latter concept refers to making a medicinal product available to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must have a MA but, either the given indication has not been authorised yet, or, although authorised, the medicinal product is not yet available on the market in this indication or clinical trials are ongoing for this indication (Article 6<sup>quater</sup>, §1, 3° Law on medicinal products and Article 108 Royal Decree of 14 December 2006 relating to medicines for human and veterinary use). Strictly spoken this does not concern the use of an unauthorised product, but an unauthorised use of an authorised medicine. As such this use concerns off-label use *sensu stricto*.

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<sup>68</sup> Guideline on compassionate use of medicinal products, pursuant to article 83 of Regulation (EC) No 726/2004, EMEA/27170/2006, July 2007.





## 2.4 Unlicensed use of medicinal products

Off-label use should formally also be distinguished from the unlicensed use of medicinal products. The term unlicensed use refers to the use of an authorised medicinal product in a different pharmaceutical form (for example, grinding a tablet into fine powder, in view of being able to administer it through a catheter with diluents added).<sup>69</sup>

However, for the purpose of this study, unlicensed use of medicinal products will be included in the scope of off-label use. Furthermore, the use of unauthorised medicines will be included in the analysis.

- **The placing on the market of medicinal products is conditioned by obtaining prior authorization. This restriction on the free movement of medicinal products is justified by the will of Governments to protect public health.**
- **The off-label use is not, as such, defined in the Community code on medicinal products for human use. The reality of the off-label use is however recognized in the guidelines and in the veterinary regulations. In practice, the term off-label use refers to the prescribing or administration of an authorized medicinal product outside any of the terms of the marketing authorisation, as reflected in the summary of product characteristics (SmPC). This might include use for a different indication, at a different dosage (or dosage frequency), duration of use, different method of administration, or use by a different patient group (for example, children or pregnant women).**
- **The off-label use should not be confused with use of unauthorized medicinal products, such as for instance drugs in clinical studies, pharmacy-made preparations, emergency situations, compassionate use and special needs.**

- **Formally, the off-label use should not be confused with the unlicensed use of drugs.**
- **A prescription should always respect the patient's rights. This includes requesting and obtaining the patient's informed consent before any medical treatment.**
- **Off-label use is an exception to the general regulation on pharmaceuticals. It falls within the scope of public health and treatment policies by practitioners but must comply with all applicable EU regulation.**

<sup>69</sup> P. L'Ecluse, C. Longeval and K. T'Syen, "Off-label use of medicinal products and product liability", *Multi-jurisdictional guide* 2013; L. Weynants, C. Schoonderbeek and C. Weyne, "Off-label Use and Promotion: Risks and Potential Liability", *Bioscience Law Review* 2010, Vol. 11, No. 4; NSW

Department of Health, *Off-label Use of Registered Medicines and Use of Medicines under the Personal Importation Scheme in NSW Public Hospitals: A Discussion Paper*, September 2003, [www.ciap.health.nsw.gov.au/nswtag/documents/publications/other-docs/off-label-use-sept-2003.pdf](http://www.ciap.health.nsw.gov.au/nswtag/documents/publications/other-docs/off-label-use-sept-2003.pdf).



### 3 LEGAL FRAMEWORK ON A EU LEVEL

#### 3.1 Primary legislation

There is very little regulation of off-label pharmaceutical use on an EU-wide basis.<sup>70</sup> According to the General Court of the European Union, “*off-label prescribing is not prohibited, or even regulated, by EU law*”.<sup>71</sup>

Primary EU-legislation, and namely article 4 of the Treaty on the Functioning of the EU (TFEU) states that “*the Union shall share competence with the Member States where the Treaties confer on it a competence which does not relate to the areas referred to in Articles 3 and 6*” and specifically refers to “*common safety concerns in public health matters, for the aspects defined in this Treaty*”. Named article 6 adds that “*the Union shall have competence to carry out actions to support, coordinate or supplement the actions of the Member States*”, where the first listed field of competence is the “*protection and improvement of human health*”.

Pursuant to Article 4(3) TFEU, public authorities are under a duty of sincere cooperation that means they must not only positively take all appropriate steps to ensure full implementation of EU law but must also actively refrain from taking measures which could hinder the full implementation of EU law, affect an EU measure or alter its scope.

Although **public health and especially the protection of public health are shared responsibilities of the Union and the Member States**, this protection of human health is **central in the EU-legislation**<sup>72</sup> and forms a specific limit to the major EU-liberties (free movement of goods, capital, services and persons) guaranteed by the TFEU.<sup>73</sup>

Bearing this in mind, article 114 (1) TFEU states that “*the European Parliament and the Council shall, acting in accordance with the ordinary legislative procedure and after consulting the Economic and Social*

*Committee, adopt the measures for the approximation of the provisions laid down by law, regulation or administrative action in Member States which have as their object the establishment and functioning of the internal market*”, providing however in paragraph 3 that “*the Commission, in its proposals envisaged in paragraph 1 concerning health, safety, environmental protection and consumer protection, will take as a base a high level of protection, taking account in particular of any new development based on scientific facts. Within their respective powers, the European Parliament and the Council will also seek to achieve this objective*”. Moreover, the absence of danger for human health should remain a basic principle in any EU policy.

In that regard, Article 168 (1) TFEU provides that “**a high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities**” and that EU action in the field of public health “*shall be directed towards improving public health, preventing human illness and diseases, and obviating sources of danger to physical and mental health*”. Furthermore and although Article 168 (5) TFEU excludes legislative harmonisation at EU level in the field of public health, it explicitly authorizes the EU in the field of public health “*to adopt binding legislation that sets high standards of quality and safety for medicinal products and devices for medicinal use*”. This EU action must, however, always “*respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care*.” The responsibilities of the Member States include “*the management of health services and medical care and the allocation of resources to them*” (Article 168 (7) TFEU).

<sup>70</sup> P. Bogaert and A. Schwabl, “Cost considerations should not drive off-label drug use in the EU”, *Scrip Regulatory Affairs*, June 2012; E. Davies et al., “A comparative review of off-label pharmaceutical use and promotion in Europe, the US and China”, Clifford Chance, October 2011.

<sup>71</sup> Case T-452/14, recital 79.

<sup>72</sup> Article 9 TFEU states that “In defining and implementing its policies and activities, the Union shall take into account requirements linked to the

promotion of a high level of employment, the guarantee of adequate social protection, the fight against social exclusion, and a high level of education, training and protection of human health”.

<sup>73</sup> Article 36 TFEU lists “*the protection of health and life of humans*” within the acceptable limitations of “*prohibitions or restrictions on imports, exports or goods in transit*”. So does article 45 and article 52 TFEU with regard to free movement of persons and the latter for the free movement of services.



The obligations of the Member States to comply with the EU pharmaceutical regime (and especially Directive 2001/83 and Regulation 726/2004), which was adopted under Article 114 TFEU (or its predecessor), are, however, not amended by the general principles under Article 168 TFEU. This is illustrated, for instance, by the ruling of the Court of Justice in *Octapharma v ANSM* (case C 512/12), stating that the Member State powers under Article 168 (4) (a) to impose more stringent protective measures related to blood do not apply to blood medicines covered by Directive 2001/83.<sup>74</sup>

Through the evolution of primary law – especially as supported by the jurisprudence of the Court of Justice – It appeared that EU health-regulation has evolved from a health-care products-approach to a more “patient-centred” approach. EU regulations recognise an increasing place to health-care and public safety and tend to consider them as autonomous fundamental rights to EU-citizens.<sup>75</sup>

Thus the Council of the European Union adopted on 1 June 2006 Council Conclusions on Common values and principles in European Union Health Systems.<sup>76</sup> This communication explicitly recalls the operating principles that underpin our health care plans “*in the sense that all EU citizens would expect to find them, and structures to support them in a health system anywhere in the EU.*”

*These include:*

— *Quality:*

*All EU health systems strive to **provide good quality care**. This is achieved in particular through the obligation to continuous training of healthcare staff based on clearly defined national standards and ensuring that staff have access to advice about best practice in quality, stimulating innovation and spreading good practice, developing systems to ensure good clinical governance, and through monitoring quality in the health system. An important part of this agenda also relates to the principle of safety.*

— *Safety:*

*Patients can expect each EU health system to secure a systematic approach to **ensuring patient safety**, including the monitoring of risk factors and adequate, training for health professionals, and protection against misleading advertising of health products and treatments.*

— *Care that is based on evidence and ethics:*

*Demographic challenges and new medical technologies can give rise to difficult questions (of ethics and affordability), which all EU Member States must answer. Ensuring that care systems are **evidence-based** is essential, both for providing high-quality treatment, and ensuring sustainability over the long term. All systems have to **deal with the challenge of prioritising health care in a way that balances the***

<sup>74</sup> See in that respect the judgment of the General Court in *Laboratoires CTRS v European Commission* (case T-452/14). The General Court considered that references in the SmPC of a medicinal product to possible effect in a non-authorized indication, would have a circumvention of the market exclusivity granted to an orphan drug. The General court stated that, since this market exclusivity is “the most significant incentive under the regulation to which an authorised orphan medicinal product is entitled”, the indication in the SmPC of effectiveness of the product for this specific off-label orphan indication would undermine the effectiveness of Article 8(1) of Regulation No 141/2000. In those circumstance, the General Court stated: “It must be held that if the effectiveness of Article 8(1) of Regulation No 141/2000 is to be ensured, the

off-label prescribing of a medicinal product for therapeutic indications covered by the market exclusivity attaching to another medicinal product by virtue of that provision should not be facilitated.” (recital 78).

<sup>75</sup> S. Engelen en P. Slegers, « Vers une Europe de la santé... », *J.D.E.*, 2011/5, n° 179, p. 125-130.

<sup>76</sup> Council Conclusions on Common Values and Principles in European Union Health Systems [http://eur-lex.europa.eu/legal-content/en/txt/?uri=CELEX:52006XG0622\(01\)](http://eur-lex.europa.eu/legal-content/en/txt/?uri=CELEX:52006XG0622(01))



**needs of individual patients with the financial resources available to treat the whole population.**

— *Patient Involvement:*

All EU health systems aim to be **patient-centred**. This means they aim to involve patients in their treatment, to be transparent with them, and to offer them choices where this is possible, e.g. a choice between different health care service providers. Each system aims to offer individuals information about their health status, and the right to be **fully informed about the treatment being offered** to them, and to consent to such treatment. All systems should also be publicly accountable and ensure good governance and transparency.

— *Redress:*

Patients should have a right to redress if things go wrong. This includes having a transparent and fair complaints procedure, and clear information about liabilities and specific forms of redress determined by the health system in question (eg. compensation).

— *Privacy and confidentiality:*

*The right of all EU citizens to confidentiality of personal information is recognised in EU and national legislation.”*

The implementation of these principles and basic rules has led the European Union to adopt regulations in the field of health products and, gradually, in the provision of health care.<sup>77</sup> Bearing those principles in mind will be guiding when evaluating off-label use of medicinal products.

In summary, the **protection of public health puts both the EU and the Member States in charge of public health protection measures**, where the definition of safety is largely adopted by Member States, under the control of the EU authorities. The EU is expressly entrusted with the task of ensuring the quality and safety of products (in this case medicines), through strict measures, which obviously must also take into account the actual use of the product. This is also reflected in the more recent developments in EU pharmaceutical law that show a growing focus on off-label use (title

3.2.3). The EU pharmaceutical regime is not only based on a principle that medicines must be of sufficient quality, safety and efficacy, but also sets very specific standards for demonstrating compliance with the principle (see 3.2.1), including the details in Annex I to Directive 2001/83 and the numerous EMA guidelines, and specific procedures for assessing that compliance.

- **The protection of human health takes a growing place in the founding principles of European law. It is a pivot value that must be taken into account in the determination of the policies of the European Union, including in its regulating efforts in the ‘harmonised’ regulation. This protection may justify a limitation of the freedoms recognized by the Treaty, particularly as regards the free movement of goods and services.**
- **Six common principles govern our health system: quality, safety, care that is based on evidence and ethics, patient involvement, redress and privacy.**
- **The protection of public health puts both the EU and the Member States in charge of public health protection measures, where the definition of safety is largely adopted by Member States, under the control of the EU authorities. This means that the EU is at least expressly entrusted with the task of ensuring the quality and safety of medicines, through strict measures, which obviously must also take into account the actual use of the product. This is also reflected in the more recent developments in EU pharmaceutical law that show a growing focus on off-label use.**

<sup>77</sup> B. Fonteyn & P. Slegers, « La directive 2011/24/UE relative à l’application des droits des patients en matière de soins de santé transfrontaliers : bien

plus qu’une codification », in *European Journal of Consumer Law*, Larcier, n° 1/2012, pp. 61-79



## 3.2 Secondary legislation

Secondary legislation is mainly based on an approach to the 'product'. It aims to regulate the free movement of products that, given their nature, have an impact on human health. Secondary legislation is an implementation of primary law, to which it necessarily relates and that also shapes the compliance measure.

### 3.2.1 Marketing authorisation is standard

As stated above, the **general rule is that a medicinal product can only be released on the market when a marketing authorisation has been issued** by the competent regulatory authority. The assessment involves establishing that a medicine's public health benefits outweigh its known risks. This is based on an evaluation of the scientific data on the quality, safety and efficacy of the product.<sup>78</sup>

Under Directive 2001/83/EC, a medicinal product can only be put on the market and promoted when it is covered by a marketing authorisation and **all promotion must "comply with the particulars listed in the summary of product characteristics"**. According to the CJEU these rules do not only apply to the pharmaceutical company marketing the product but, in principle, to all persons because *"even where it is carried out by an independent third party outside any commercial or industrial activity, advertising of medicinal products is liable to harm public health"*<sup>79</sup> (see more details on promotion of off-label use in title 3.2.2).

The regulation of the pharmaceutical products market is driven by an overall protection of public human health. Restrictions to the distribution and marketing of medicines are justified by this high protection of major interest. However, case-law only validates regulatory restrictions to the extent that this restriction is necessary and proportionate to achieve the protection of human health and safety. Therefore, the limitation of access to registered medicines through a prior MA, should be considered as the most appropriate way to ensure the balance between protection of public health and the freedom for undertakings which develop and market such products. Given this balance, exceptions to this prior authorisation shall be evaluated accordingly.<sup>80</sup>

Consequently, there are **very limited exceptions to the marketing authorisation requirement** provided for in Directive 2001/83/EC. Those exceptions are of three kinds:<sup>81</sup>

- magisterial and officinal formulae (Art. 3(1) and (2) of Directive 2001/83/EC);
- medicinal products in authorised clinical trials (Art. 3(3) of Directive 2001/83/EC);
- medicinal products in medical need situations – i.e. when one of the specific exceptions listed in either Directive 2001/83/EC or Regulation 726/2004/EC applies, e.g.
  - special need exemption (Art. 5(1) of Directive 2001/83/EC);<sup>82</sup>
  - emergency situation (Art. 5(2) and (3) of Directive 2001/83/EC);

<sup>78</sup> European Commission, Health and Consumers Directorate-General, Volume 2A Procedures for marketing authorisation, Chapter 1 Marketing Authorisation, [http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a\\_chap1\\_2013-06\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_2013-06_en.pdf); P. Bogaert and A. Schwabl, "Cost considerations should not drive off-label drug use in the EU", *Scrip Regulatory Affairs*, June 2012.

<sup>79</sup> Case C-421/07, CJEU, Damgaard [2009] ECR I-2629, paragraph 22 and paragraph 29.

<sup>80</sup> See hereunder, part 3.4 EU case law.

<sup>81</sup> J. Killick and P. Berghe, "Does promoting off-label use of medicines on budgetary grounds risk jeopardising the integrity of the marketing

authorisation requirement system?", *Pharmaceutical Law Insight*, December 2009, Vol. 6(1).

P. Bogaert and A. Schwabl, "Cost considerations should not drive off-label drug use in the EU", *Scrip Regulatory Affairs*, June 2012.

EFPIA, *Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals*, [www.eesc.europa.eu/self-and-coregulation/documents/codes/private/122-private-act.pdf](http://www.eesc.europa.eu/self-and-coregulation/documents/codes/private/122-private-act.pdf).

<sup>82</sup> This exception is intended to fulfil 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 use.

- and compassionate use, where there is no other treatment available (Art. 83 of Regulation 726/2004/EC).

Bearing in mind the above equilibrium between health protection and industrial freedom, **exemptions from the MA requirement should be interpreted restrictively.**<sup>83</sup>

'In accordance with the situation of prescription of an unauthorised medicinal product, **EU pharmaceutical law does not preclude the prescription of an authorised product for an un-authorized modality ("off-label" prescription) at the discretion of the doctor and at his own responsibility**'.<sup>84</sup> As recognized by the Commission, this off-label exception derives from the general principle of therapeutic freedom for prescribing physicians.<sup>85</sup> It therefore fits in the overall obligation to ensure an adequate protection of human health – where this implies that **restricting the use of products only to registered indications despite the fact that the product can prove its effectiveness and safety would be an unreasoned limitation of the access to possible treatment to patients.**

However, any authorisation for a broader off-label use is not clearly provided by EU law. The insertion of provisions 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 emphasise this as off-label use is not mentioned (see also chapter 2.3.) Article 5(3), however, does refer to the use of a medicinal product otherwise than for the authorised indications. The exceptional nature of off-label also finds confirmation in the fact that off-label use is not accepted as a satisfactory method of treatment for the application of Article 3(1)(b) of Regulation 141/2000/EC of the European Parliament and of the Council on orphan medicinal products (Regulation 141/2000/EC).<sup>86</sup> Off-label seems thus only possible in specific

circumstances where a patient needs special treatment. Off-label use fits into the overall obligation to put the patients' health and safety central.

- **The primary purpose of the rules governing medicinal products is to safeguard public health. This objective must be achieved by means which do not hinder the development of the pharmaceutical industry or trade in medicinal products within the Union. Thus, the pharmaceutical legislation of the European Union has consistently pursued the twin objectives: the protection of public health and the free movement of medicinal products.**
- **Product regulation – including pharmaceutical products regulation – is part of the regulatory measures put in place to ensure a balanced protection of the human health, taking into account the named free movement of goods.**
- **The use of medicinal products without authorisation is referred in a limited way in the European legislation on medicinal products. Otherwise, these assumptions would contrast with the restrictions related to the requirement of a prior marketing authorization.**
- **The off-label use of medicinal products fits in the larger framework of public health policy, patient's safety and adequate treatment.**
- **EU pharmaceutical law does not preclude the off-label prescription at the discretion of the doctor and at his own responsibility. This exception is an application of the general principle of therapeutic freedom for prescribing physicians.**

<sup>83</sup> This was recently confirmed by the CJEU in *Commission v Poland* which is discussed below (Case C-185/10, *Commission v. Poland* [2012]).

J.E. Osborn, "Can I tell you the truth? A comparative perspective on regulating off-label scientific and medical information", *Yale Journal of health policy, Law and Ethics*, 2010; S. Oberman, "Off-Label Use of Medicines – General Aspects, Challenges and Strategies", master thesis, 2013.

<sup>84</sup> T. Tsang, "Supply of unlicensed medicines on economic grounds as a cost containment measure could not be justified according to EU court of justice", *Arnold & Porter(UK) LLP*, April 2012.

<sup>85</sup> See Commission's merger decision *Sanofi-Aventis/Zentiva* of 4 February 2009, COMP/M.5253, [http://ec.europa.eu/competition/mergers/cases/decisions/m5253\\_20090204\\_20212\\_en.pdf](http://ec.europa.eu/competition/mergers/cases/decisions/m5253_20090204_20212_en.pdf), footnote 6.

<sup>86</sup> J. Killick and P. Berghe, "Does promoting off-label use of medicines on budgetary grounds risk jeopardising the integrity of the marketing authorisation requirement system?", *Pharmaceutical Law Insight*, Dec 2009, Vol. 6(1).



### 3.2.2 Off-label promotion is generally banned

The promotion of medicinal products is strictly regulated. The underlying reason for this strict regulation is that advertising is considered to be a powerful tool which can have adverse effects on public health when excessive and ill-considered.<sup>87</sup>

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” (Article 86 of Directive 2001/83/EC).

The general principles of advertising listed in Article 87 of Directive 2001/83 include that:<sup>88</sup>

- unlicensed medicinal products must not be advertised;
- unlicensed indications for an authorised medicinal product cannot be advertised;
- prescription-only medicines may only be advertised to those persons who are qualified to prescribe or supply them;
- over the counter medication medicines may be advertised to the general public to specific rules;
- advertising must be consistent with the SmPC; and
- advertising should encourage the rational use of medicine by presenting it objectively, and it must not be misleading or exaggerate its properties.

Promoting the prescription of a pharmaceutical product for a purpose that has not been authorised is thus in principle prohibited.

In many European countries, the control on medicine advertising is primarily conducted on a self-regulatory basis. This self-regulation is conducted by the industry bodies at a national level, as well as by the body of the prescription pharmaceutical industry in Europe, the European Federation of Pharmaceutical Industries and Associations (EFPIA). 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 EFPIA established a “Code of Practice on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals”.<sup>89</sup> This Code reflects the requirements of Directive 2001/83/EC and provides a more detailed framework that can be used as a reference document by all Member State private associations.<sup>90</sup>

As Member States are required to implement adequate and effective methods to monitor the advertising of medicinal products including legal provisions (Article 97(1) of Directive 2001/83/EC), the consequences of illegally promoting off-label use depend on the national laws of the Member States. In Germany for example, the healthcare supervisory authorities can impose administrative fines to manufacturers of up to 50.000 EUR per case. However, such administrative actions have been applied very rarely. Nevertheless, there have been extensive litigations between pharmaceutical companies illegally promoting off-label use of their drug and their competitors, consumers and fair trade protection organizations. At present, the risks for manufacturers seem to be comparatively low and do not exceed the costs of a marketing campaign.<sup>91</sup>

<sup>87</sup> Recital 45 to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

<sup>88</sup> M. Smillie et al., “Advertising Medicinal Products for Human Use” in S. Shorthose (ed.) *Guide to EU Pharmaceutical Regulatory Law*, 2013, Kluwer Law International.

<sup>89</sup> EFPIA Code on the Promotion of Prescription-Only Medicines to, and Interactions with, Healthcare Professionals, [www.eesc.europa.eu/self-and-coregulation/documents/codes/private/122-private-act.pdf](http://www.eesc.europa.eu/self-and-coregulation/documents/codes/private/122-private-act.pdf).

<sup>90</sup> J.E. Osborn, “Can I tell you the truth? A comparative perspective on regulating off-label scientific and medical information”, *Yale Journal of health policy, Law and Ethics*, 2010; S. Oberman, “Off-Label Use of Medicines – General Aspects, Challenges and Strategies”, master thesis, 2013.

<sup>91</sup> E. Davies et al., “A comparative review of off-label pharmaceutical use and promotion in Europe, the US and China”, Clifford Chance, October 2011; available from: [www.cliffordchance.com](http://www.cliffordchance.com).





Off-label promotion may however also raise product liability claims, since EU product liability law operates a strict liability regime. This area seems a more relevant area of concern for the manufacturers that promote the off-label use of their products as manufacturers can be held liable even without fault (see 5.1.1). It is noteworthy that off-label promotion is vigorously prosecuted in the United States which generated the last years many billions of dollars in fines and settlements (for ex. \$2.2 billion fine for Johnson and Johnson and a \$1.19 billion criminal fine for Pfizer).<sup>92</sup> A FDA draft guidance tries to clarify the difference between “off-label marketing”, implying the sharing of information with the intent to impact sales and “off-label communications” meaning sharing information to improve and advance the public health.<sup>93</sup> The draft guidance addresses the ability for pharmaceutical firms to share truthful, scientifically accurate and data-supported information with healthcare professionals to inform treatment decisions.<sup>94</sup>

In the *Damgaard* case<sup>95</sup> the CJEU made it clear that the above mentioned provisions of EU law on advertising and promotion of medicinal products do not only apply to the pharmaceutical company marketing the drug but also to third parties acting outside any commercial or industrial activity. **Those provisions, however, do not apply to national health authorities** which are responsible to ensure that the provisions of Directive 2001/83/EC are applied and are also charged with defining the public health policy priorities. This is demonstrated in the *ABPI* case<sup>96</sup> where the CJEU held that its approach in the *Damgaard* case could not be applied in a case where **public authorities need to disseminate information about a medicinal product**. Similarly regarding financial inducements, the CJEU held that “*although the prohibition in Article 94(1) of Directive 2001/83 may admittedly apply to independent third parties who are not acting for commercial or industrial purposes or not for profit-making purposes, such a prohibition cannot apply*

*to national public health authorities, which are responsible, inter alia, (i) for ensuring that the existing rules, of which that directive forms part, are applied and (ii) for **defining the priorities for action in relation to public health policy, in particular so far as concerns the rationalisation of the public expenditure allocated to that policy which is precisely what they are responsible for***.”<sup>97</sup>

The fact that the respective advertising regulations do not bind authorities, does not, however, form by itself, a sufficient legal basis for the competence of authorities to engage in active promotion of off-label use. Actions or policies by authorities do need to rest on a proper legal basis.

Article 87 of Directive 2001/83/EC, has been interpreted by the Court of Justice in its judgment of 5 May 2011 in *Novo Nordisk*. The Court of Justice, in that case, held that no part of an advertisement for medicinal products may ever suggest, inter alia, therapeutic indications, pharmacological properties, or other characteristics that conflict with the summary of the product characteristics approved by the competent authorities upon granting marketing authorisation for that medicinal product. However, the Court of Justice also held that Article 87(2) of Directive 2001/83 cannot be interpreted as requiring that all claims in advertisements for medicinal products directed at persons qualified to prescribe or supply them have to be included in that summary of product characteristics or be derivable from information in that summary. Therefore, the General Court stated in the recent *Laboratoires CTRS*-case, that “Article 87(2) does not preclude advertising which, in keeping with the SmPC, makes statements as to the efficacy of [a medicinal product in off-label indications]”. However, according to the same judgment, an official action, such as in casu, the inclusion of statements in the SmPC and the assessment report relating to the efficacy of a medicinal product in

<sup>92</sup> Department of Justice, Office of Public Affairs: “Johnson & Johnson to Pay More Than \$2.2 Billion to Resolve Criminal and Civil Investigations”, [www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations](http://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations); D. EVANS, “Pfizer Broke the Law by Promoting Drugs for Unapproved Uses”: 9 November 2009, [www.bloomberg.com/apps/news?pid=newsarchive&sid=a4yV1nYxCGoA](http://www.bloomberg.com/apps/news?pid=newsarchive&sid=a4yV1nYxCGoA).

<sup>93</sup> “Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices” (the “Draft Guidance”). See 79 Federal Register 11793 (3 March 2014).

<sup>94</sup> <http://www.mmm-online.com/features/fda-policy-is-off-label-on-the-table/article/410554/>

<sup>95</sup> Case C-421/07, *Damgaard* [2009] ECR I-2629, paragraph 22 and paragraph 29.

<sup>96</sup> Case C-62/09, *Association of the British Pharmaceutical Industry* [2010] ECR I-3603.

<sup>97</sup> Case C-62/09, point 32.



a non-authorised indication, is liable to circumvent the aim of the pharmaceutical regulation and to render those provisions ineffective.<sup>98</sup> This is in particular the case when such an action may affect the decision the physician must take (based on patient specific therapeutic considerations). As such exclusive responsibility of the treating physician should not be interfered with:

*“The point must also be made that off-label prescribing is the sole responsibility of the prescribing physician.<sup>99</sup> That responsibility could in practice be attenuated by the presence, in a medicinal product’s marketing authorisation, of statements that the product is effective and safe for treating other therapeutic indications than those for which its marketing authorisation has been granted.”*

Although this individual case does not concern a promoting national authority, the principle that an official action should refrain from circumventing the aim of the pharmaceutical regulation is in line with the duty of sincere cooperation. This implies that Member States must not only positively take all appropriate steps to ensure full implementation of EU law but must also actively refrain from taking measures which could hinder the full implementation of EU law, affect an EU measure or alter its scope, and to the principle of effectiveness of the EU regulation. Off-label promotion, as far as it circumvents the aim of the pharmaceutical regulation and hampers the effectiveness of those provisions is thus precluded.

This does not imply, however, that public authorities are prohibited to generate and provide factual scientific information on the off-label use. The communication of (available or generated) study results of the off-label used product, without any statement on the recommended use of the off-label application seems in that respect in conformity with the respective EU legal framework. It fits in the objective which national authorities pursue: guarantee a high level of protection of health and safety, without unduly

interfering with the pharmaceutical legal framework nor in trade relations on the market.

It should be noted that in medical practice, clinical practice guidelines assist healthcare practitioners in the decision-making on the treatment of an individual patient. Clinical practice guidelines are, however, never binding for healthcare professionals.<sup>100</sup> If in the individual case, a physician considers that it is justified to derogate from a clinical practice guideline, nothing prevents him/her to do so. In that sense the decision to adhere to guidelines remains within the practitioner’s responsibility.

- **The advertising of medicinal products falls within the product regulation and is therefore also highly regulated. The European medicines regulation aims expressly banning commercial advertising for unauthorized drugs and for unauthorized uses of drugs. The advertising of medicinal products must be primarily informative and based on approved data. Infringements of the rules relating to the advertising of medicinal products are subject to enforcement procedures and measures in the different Member States.**
- **Case-law has clarified that the advertising includes also promotion activities, which are conducted by a third party to the holder of the authorisation for placing on the market. Member State medicines authorities are not covered by this extension. Yet, according to the Laboratoires CTRS - case, the prescribing doctor’s personal responsibility should not be attenuated by the presence, in a medicinal product’s MA of statements that a product is effective and safe for treating off-label indications.**

<sup>98</sup> Case T-452/14, Laboratoires CTRS v Commission, § 78 and 81

<sup>99</sup> see, to that effect, judgment of 11 April 2013 in Novartis Pharma, C 535/11, ECR, EU:C:2013:226, paragraph 48

<sup>100</sup> Vinck I, Paulus D, Van Brabant H, Ramaekers D. Medico—legale aspecten van klinische praktijkrichtlijnen. Brussel: Federaal Kenniscentrum voor de



- **The competent authorities should refrain from taking actions that would undermine the effectiveness of the pharmaceutical regulation.**
- **Member States are free, however, to provide neutral scientific information regarding off-label used products.**

### 3.2.3 Increased attention to off-label use in pharmacovigilance rules

Despite the fact that off-label use is not directly regulated and forms a specific modality exception of the general regulatory requirements for medicinal products in the broader framework of health-care providing tools, there is a particular increasing EU attention to off-label use in the legal framework for the new pharmacovigilance system in the European Union which is set out in Directive 2010/84/EU amending, as regards pharmacovigilance, the Directive 2001/83/EC (Directive 2010/84/EU).<sup>101</sup>

1. Firstly, Directive 2010/84/EU clearly states: “As medicinal products could be used outside the terms of the marketing authorisation, the marketing authorisation holder’s responsibilities should include providing all available information, including the results of clinical trials or other studies, as well as **reporting any use of the medicinal product which is outside the terms of the marketing authorisation.** It is also appropriate to ensure that all **relevant information collected on the safety** of the medicinal product is taken into account when the marketing authorisation is being renewed” (recital 12 of Directive 2010/84/EC).

Consequently the Directive has widened the scope of adverse reactions to “ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product” (recital 5 of Directive 2010/84/EU).

In this regard recital 17 of the Directive gives a clear view of the tasks of the Member States: “Member States should operate a

pharmacovigilance system to collect information that is useful for the monitoring of medicinal products, **including information on suspected adverse reactions** arising from use of a medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, including overdose, misuse, abuse and medication errors, and suspected adverse reactions associated with occupational exposure”.

The Directive also stressed the importance of **direct patient reporting** (DPR). DPR refers to the possibility for patients to report directly suspected adverse drug reactions to competent authorities. This applies also for off-label indications. DPR is already in place in several EU countries, but the systems are rather different and some of them are more developed than others. Therefore Member States should facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats (article 102 (b) Directive 2010/84).

2. Secondly, in parallel with the broadening of the scope of adverse effects, the new definition of a post-authorisation safety study in Directive 2010/84/EU now reads as follows: “any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures”. Previously, a post-authorisation safety study was defined in Article 1(15) of Directive 2001/83/EC as “a *pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product*”. The definition of a post authorisation safety study is no longer limited to a study carried out in accordance with the terms of the marketing authorisation. Consequently, **regulators can require that firms conduct a post authorisation safety study covering the off-label use.**

<sup>101</sup> OJ L 348, 31.12.2010, p. 74.



3. Thirdly, in accordance with Article 23 of Directive 2001/83/EC and Article 16 of Regulation 726/2004/EC, marketing authorisation holders are obliged to ensure that the product information is kept up to date with the current scientific knowledge. The **Regulatory Authorities must thus be informed of any new information** which might influence the evaluation of the benefits and risks of the medicinal product concerned, including **“both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation”**.<sup>102</sup>
4. Fourthly, the Directive replaced Article 116 of Directive 2001/83/EC. This Article now provides that the competent authorities shall suspend, revoke or vary a marketing authorisation when the risk-benefit balance is not favourable. The previous version of the Article stated that competent authorities *“shall suspend or revoke an authorisation to place a medicinal product on the market where that product proves to be harmful in the normal conditions of use referred to the risk-benefit balance not being positive”*.<sup>103</sup>

These references are fully in line with the principles as they result from the above mentioned Council Conclusions on Common values and principles in European Union Health Systems.

- **The European pharmaceutical law provides more attention to off-label use in its pharmacovigilance system.**
- **Since the implementation of the 2010 pharmacovigilance revision the MAH is obliged to report adverse drug reactions associated with off-label uses to the agencies. The new pharmacovigilance Directive clearly recognises 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.**

<sup>102</sup> EMA, Guideline on the processing of renewals in the centralised procedure, EMEA/CHMP/2990/00 Rev. 4, 22 June 2012.

### 3.3 Regulatory aspects on a EU level

#### 3.3.1 Extension of marketing authorisation regulation

Once a medicinal product has been granted an initial marketing authorisation in accordance with Article 6 of Directive 2001/83/EC *“any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1)”* (Article 6 (2) Directive 2001/83/EC). However, any change made to a product dossier, must be notified to the competent authorities of the Member States where the medicinal product is authorised.

The words “variations and extensions” are taken from Regulation 1234/2008/EC concerning the examination of variations to the terms of MA for medicinal products for human use and veterinary medicinal products (Regulation 1234/2008/EC).<sup>104</sup> According to this Regulation the procedural steps to introduce a variation depend on the type of variation.

**Certain changes to a MA have to be considered to fundamentally alter the terms of the MA** and therefore cannot be granted following a variation procedure. These specific changes, defined in Annex I of the Regulation, **are considered to be “extensions”**:

1. Changes to the active substance(s)
2. Changes to strength, pharmaceutical form and route of administration
3. Other changes specific to veterinary medicinal products to be administered to food-producing animals; change or addition of target species

<sup>103</sup> See also Article 117 Directive 2001/83/EC.

<sup>104</sup> OJ L 334, 12.12.2008, p. 7.





According to the nature of the extension, the extension applications are processed in accordance with the standard procedures for granting a MA.

However, changes to introduce a **new therapeutic indication or to modify an existing one** as well as variations related to significant modifications of the SmPC (e.g. inclusion of a new target population, changes in posology etc.) **are classified as major variations** of Type II (annex II of Regulation 1234/2008/EC).

A new indication must be understood as:<sup>105</sup>

- a new target disease
- different stages or severity of a disease
- an extended target population for the same disease, e.g. based on a different age range or other intrinsic (e.g. renal impairment) or extrinsic (e.g. concomitant product) factors
- change from the first line treatment to second line treatment (or second line to first line treatment), or from combination therapy to monotherapy, or from one combination therapy (e.g. in the area of cancer) to another combination,
- change from treatment to prevention or diagnosis of a disease
- change from treatment to prevention of progression of a disease or to prevention of relapses of a disease
- change from short-term treatment to long-term maintenance therapy in chronic disease.

Where a major variation of Type II is made, the marketing authorisation holder must submit a Type II application. Applications must be accompanied by relevant documents and data in support of the variation. Variations in the indications of use must also be supported by clinical and pre-clinical data, if justified.<sup>106</sup>

The procedural effort and cost of such a variation is relatively low and strictly regulated.<sup>107</sup> However pharmaceutical companies may lack incentives to develop new or variations of the indications.

There are several barriers that hinder the development of new indications or variations of existing indications. The **current legal infrastructure of medicine patents and regulatory exclusivity periods is primarily designed to promote the development of new medical products, not new indications for existing products.** As such, the business model of the pharmaceutical industry revolves around patent rights and exclusivity periods. Consequently, these companies often stop testing drugs for new indications long before the patent term expires because the necessary clinical trials for a new indication take many years to complete and firms need time on the market to recoup their R&D investment. The same goes for generic companies. It makes no sense to invest in the clinical development of generic drugs if there is no foreseeable return on investment.<sup>108</sup> The European legislator attempted to come forward to this issue for the authorisations of new indications by (possibly) granting a non-cumulative period of one year of data exclusivity (see for more details 3.3.2.1).

<sup>105</sup> European Commission, Enterprise and Industry Directorate-General, Guidance on new elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period. [http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline\\_14-11-2007\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline_14-11-2007_en.pdf)

<sup>106</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q\\_and\\_a/q\\_and\\_a\\_detail\\_000026.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000026.jsp)

<sup>107</sup> European Commission, Enterprise and Industry Directorate-General, *Guidance on a new therapeutic indication for a well-established substance*, November 2007, [http://ec.europa.eu/health/files/eudralex/vol-2/c/10%20\\_5\\_%20guideline\\_11-2007\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/10%20_5_%20guideline_11-2007_en.pdf).

<sup>108</sup> R.S. Stafford, "Regulating off-label drug use – Rethinking the role of the FDA", *N Engl J Med*, 2008; C.J J. Mulder, D.P. van Asseldonk, N.K.H. de Boer, "Drug Rediscovery to Prevent Off-Label Prescription Reduces Health Care Costs: the Case of Tioguanine in The Netherlands", *J Gastrointestin Liver Dis*, June 2014 Vol. 23 No 2; B.N. Roin, *Solving the problem of new uses by Creating Incentives for Private Industry to Repurpose Off-Patent Drug*, draft 15 September 2014, [http://petrieflom.law.harvard.edu/assets/publications/Roin\\_Solving\\_the\\_Problem\\_of\\_New\\_Uses.pdf](http://petrieflom.law.harvard.edu/assets/publications/Roin_Solving_the_Problem_of_New_Uses.pdf).



Another factor hindering the development of new indications or variations of existing indications is that off-label prescribing is widely practiced and recommended throughout the medical society. It is particularly common in the areas of oncology, obstetrics, and infectious disease (HIV/AIDS) and in the care of children, pregnant women or palliative care. As a consequence, the cost of the usually long and laborious clinical development process required for demonstrating efficacy and safety of a new indication of an already approved medicine might simply not be worth the possible financial return. This economic disincentive is even greater in the relatively small markets for orphan and paediatrics indication where recruitment problems may occur.<sup>109</sup> Furthermore, off-label use often already generates an income for pharmaceutical companies since it will often be possible to bill it as on-label used pharmaceuticals. In addition, there might be several mechanical, ethical and legal obstacles that makes the manufactures reluctant to conduct these test, e.g. problems with the informed consent in special patient groups.<sup>110</sup>

- **Drug regulation organises the evolution and the extension of an authorisation of placing a medicinal product on the market. Changes to introduce a new therapeutic indication or to modify an existing one as well as variations related to significant modifications of the SmPC (e.g. inclusion of a new target population, changes in posology etc.) are classified as major variations for which relevant documents and data in support of the variation need to be submitted.**

- **Because of the practical impact of off-label use, intellectual property law does (often) not effectively promote the development of new indications for existing drugs, in contrast to the development of new molecules. As a result, from an economic point of view, the R&D cost to provide evidence in these new indications may not be recovered.**
- **Yet, the off-label use is widespread, in particular in some therapeutic areas (Oncology, Pediatrics, etc.).**

### 3.3.2 Incentives to encourage further development

As stated above, preclinical and clinical trials are expensive and time consuming and often require significant investment from the originator companies. However, the European legislators have created incentives in order to encourage the further development of already authorised medicinal products.<sup>111</sup>

#### 3.3.2.1 Data exclusivity

In 2005, the EU **Data Exclusivity Directive**<sup>112</sup> was brought into force. Article 10 (1) paragraph 4 of Directive 2001/83/EC provides a harmonized data exclusivity period for all the Member States. The exclusivity period is "8+2+1" years. A pharmaceutical firm introducing its product to market in the EU can thus enjoy eight years of data exclusivity,<sup>113</sup> two years of marketing

<sup>109</sup> To meet this difficulty, the European authorities have implemented measures for paediatric medicines. The success of these measures (PUMAs) is, however, limited, as evidenced in the report of 2013 of the European Commission in the Parliament (COM (2013) 443).

<sup>110</sup> A. Wertheimer, "Off-label prescribing of drugs for children", *Current Drug Safety* 2011, 6; A.T. Tabarrok, "Assessing the FDA via the anomaly of off-label drug", *Independent Review* 2000, 5(1); B.N. Roin, *Solving the problem of new uses by Creating Incentives for Private Industry to Repurpose Off-Patent Drug*, draft 15 September 2014, [http://petrieflom.law.harvard.edu/assets/publications/Roin\\_Solving\\_the\\_Problem\\_of\\_New\\_Uses.pdf](http://petrieflom.law.harvard.edu/assets/publications/Roin_Solving_the_Problem_of_New_Uses.pdf).

<sup>111</sup> Carolyne Hathaway, John Manthei and Cassie Scherer. *Exclusivity Strategies in the United States and European Union* [http://www.lw.com/upload/pubcontent/\\_pdf/pub2655\\_1.pdf](http://www.lw.com/upload/pubcontent/_pdf/pub2655_1.pdf)

<sup>112</sup> Directive 2004/27/EC, amending Article 10 of Directive 2001/83/EC (OJ L 136, 30.04.2004, p. 34).

<sup>113</sup> Period of time during which a Company cannot cross-refer to the data in support of another marketing authorisation, i.e.: generics, hybrids, biosimilars cannot be validated by the EMA. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2013/05/WC500143122.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143122.pdf)



exclusivity<sup>114</sup> and a one year extension. Two types of possible extended marketing protection can be distinguished.

- New indication for a relatively new product (art. 10 (1) Directive 2001/83/EC)

The ten years period **protection is extended to a maximum of eleven years if during the first eight years of the ten years of protection, the MA holder obtains an MA for one or more new therapeutic indications which are held to bring a significant clinical benefit in comparison to existing therapies in the new therapeutic indication.**<sup>115</sup> The **additional year of marketing protection applies to the global marketing authorisation for the reference medicinal product.** Generic products, with or without the new therapeutic indication, may not be placed on the market until expiry of the eleventh year.<sup>116</sup>

The notion existing therapies refers to satisfactory methods of diagnosis, prevention or treatment of the disease in question and can include authorized medicinal products as well as other established methods (e.g. psychotherapy, other "state of the art" therapeutic methods for the indication). In order to demonstrate significant clinical benefit the MAH should provide scientific data and documentation establishing that the medicinal product for which the extended marketing protection is sought is of significant clinical benefit in comparison with existing therapies. This justification should in general be supported by results of comparative clinical studies.

As the additional year of marketing protection applies to the global marketing authorisation for the reference medicinal product, the one year extension may be very valuable if there is no (longer) effective coverage by a patent.

- New indication for a well-established product (art. 10 (5) Directive 2001/83/EC)

**A new indication for a well-established substance (normally a substance approved for at least ten years) triggers a one-year data exclusivity period if significant pre-clinical or clinical studies in relation to the new indication were conducted.**

The significance of the preclinical or clinical studies will be assessed by the EMA on a case-by-case basis.<sup>117</sup>

In principle, when applying for marketing authorisation for a new indication, it is expected that the applicant has carried out at least one confirmatory clinical trial versus a suitable comparator in the new indication. This trial would be considered as a significant clinical study. However, as standard requirements for granting a marketing authorisation for a new indication are applicable, further data including preclinical or clinical pharmacological and further confirmatory clinical trial(s) may also be required for granting a marketing authorisation.

Exceptionally, other preclinical or clinical studies performed by the applicant could be considered significant if they allowed the use of existing or published data (e.g. clinical trials) to support the marketing authorization application in the new indication.

<sup>114</sup> This is the period of time during which a generic company may not market an equivalent generic version of the originator's pharmaceutical product (although their application for authorisation may be processed during this period, such that they are in a position to market their product on the expiry of this additional 2 year period).

<sup>115</sup> See European Commission, Enterprise and Industry Directorate-General, Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period, November 2007. [http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline\\_14-11-2007\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline_14-11-2007_en.pdf)

<sup>116</sup> European Commission, Health and Consumers Directorate-General, Volume 2A Procedures for marketing authorisation, Chapter 1 Marketing Authorisation, [http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a\\_chap1\\_2013-06\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_2013-06_en.pdf).

<sup>117</sup> See European Commission, Enterprise and Industry Directorate-General, Guidance on a new therapeutic indication for a well-established substance, November 2007. [http://ec.europa.eu/health/files/eudralex/vol-2/c/10%20\\_5\\_%20guideline\\_11-2007\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/10%20_5_%20guideline_11-2007_en.pdf)



The additional year of marketing protection for older well established substances seems to be not an effective incentive. One year after the MA is typically too short to recoup the investment.

According to data published by the EMA, 244 extensions of indications for 127 products were granted by the EMA between 2004 and 2011 and only eight extensions of market exclusivity were approved, while six applications were rejected between 2008 and 2012.<sup>118</sup>

A limited extension of monopoly protection allows a faster generic entry at the expense of drug repurposing. Once pharmaceutical companies lose the monopoly protection and generics enter, patients will use the low-cost generics regardless of whether they are taking the drug for an old or new indication. As such, pharmaceutical companies will have no incentives to invest in the development of new indications for 'old' drugs. Yet, an argument to withhold prolonged patent protection as a reward for drug repurposing may be the fear that if firms could delay generic entry by developing new uses for their drugs, they might hold off generic competition indefinitely by continually developing minor new indications with little therapeutic value.

In the US method-of-use patents are granted over newly discovered indications for FDA-approved drugs ("new use patents"). These rights provide the patent holder with a monopoly over the act of taking or administering the existing drug for the new indication. This monopoly has, however, little meaning once generics are on the market since pharmaceutical companies lack the information whether physicians prescribe drugs for patented indications. Since physicians do not disclose the indications for their prescriptions to pharmaceutical companies, they rarely have access to the information needed to enforce new use patents if generics are available.<sup>119</sup>

<sup>118</sup> Z. Frias (EMA), *Data exclusivity, market protection and paediatric rewards, Workshop for Micro, Small and Medium Sized Enterprises*, April 2013, [www.ema.europa.eu/docs/en\\_GB/document\\_library/Presentation/2013/05/WC500143122.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143122.pdf).

<sup>119</sup> Benjamin N. Roin. Solving the problem of new uses by creating incentives for private industry to repurpose off-patent drugs. Draft 15 September 2014 DRUGS

### 3.3.2.2 Orphan drugs

The EU **Orphan drug Regulation** 141/2000/EC, became effective in 2000. This EU legislation aims to encourage access to medicines for rare diseases (affecting not more than five in ten thousand persons in the EU) by **providing incentives for the research, development and marketing of orphan medicinal products** that the pharmaceutical industry would be unwilling to develop under normal market conditions.

Sponsors of designated orphan medicines are eligible to benefit from the following incentives:<sup>120</sup>

- Assistance with development of the medicine (protocol assistance);
- Reduced fees for pre-authorisation and post-authorisation activities;
- Supporting research by providing funds;
- Protection from market competition once the medicine is authorized by offering a market exclusivity of 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.

In the *Laboratoires CTRS v. European Commission* case, the general court stated that, since this market exclusivity is "the most significant incentive under the regulation to which an authorised orphan medicinal product is entitled", the indication in the SmPC of effectiveness of the product for a specific off-label orphan indication would undermine the effectiveness of Article 8(1) of Regulation No 141/2000.<sup>121</sup>

[http://petrieflom.org/assets/publications/Roin\\_Solving\\_the\\_Problem\\_of\\_New\\_Uses.pdf](http://petrieflom.org/assets/publications/Roin_Solving_the_Problem_of_New_Uses.pdf)

<sup>120</sup> R.R. Shah, "Fabry Disease: Perspectives from 5 Years of FOS - Chapter 11 Regulatory framework for the treatment of orphan diseases", *Oxford Pharma Genesis*, 2006; EMA, *Medicines for rare diseases*, [www.ema.europa.eu/ema/index.jsp?curl=pages/special\\_topics/general/general\\_content\\_000034.jsp&mid=WC0b01ac058002d4eb](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000034.jsp&mid=WC0b01ac058002d4eb).

<sup>121</sup> Case T-452/14, *Laboratoires CTRS v. Commission*, §77



### 3.3.2.3 Paediatric Medicines

Finally, Regulation 1901/2006/EC (**Paediatric Regulation**), which became effective in 2007, sets up a system of obligations, rewards and incentives, together with horizontal measures **to ensure that medicines are regularly researched, developed and authorized to meet the therapeutic needs of children.**

The Regulation is addressed to:

- The pharmaceutical industry by setting out the legal framework for receiving rewards and incentives by conducting clinical trials in the paediatric population. The Regulation provides sponsors with the right to apply for a six month extension to the product's supplementary protection certificate (SPC) in return for conducting pediatric studies on the product.
- The Member States to set out to support research into, and the development and availability of, medicinal products for paediatric use;
- The EU as funds for research into medicinal products for the paediatric population shall be provided for in the EU budget in order to support studies relating to medicinal products or active substances not covered by a patent or a supplementary protection certificate.<sup>122</sup>

Paediatric-use marketing authorisations (PUMAs) are a type of marketing authorisation that covers the indication and appropriate formulation for the paediatric population.<sup>123</sup> PUMAs were introduced by the Paediatric Regulation. Companies can request PUMAs for medicines that are:

- already authorised;
- no longer covered by intellectual property rights (patents or supplementary protection certificates);
- to be exclusively developed for use in children.

The development of medicines in children must follow a paediatric investigation plan (PIP) must discuss all paediatric subsets, as agreed by the Paediatric Committee (PDCO).

A PUMA will benefit from 10 years of market protection as a reward for the development in children.

According to the "Progress report on the paediatric regulation (EC N°1901/2006" (COM (2013) 443), the PUMA concept appeared to be disappointing.<sup>124</sup> This is confirmed in literature where it was demonstrated that the off-label prescribing and the use of unlicensed products in paediatrics did not decrease after the implementation of the PUMAs.<sup>125</sup> It might be too early, however, to make a sound assessment of the overall impact. On the other hand, public funding of research appeared to be promising.

- **Several recent developments in pharmaceutical regulation incorporate incentives to R&D activities, including such activities on existing products. This is supported by regulations on data exclusivity, orphan medicinal products and paediatric medicines.**

<sup>122</sup> B. Lehman, "Regulation (EC) No 1901/2006 on medicinal products for paediatric use & clinical research in vulnerable populations", *Child and Adolescent Psychiatry and Mental Health* 2008.

<sup>123</sup> [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000068.jsp&mid=WC0b01ac0580025b8b](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp&mid=WC0b01ac0580025b8b)

<sup>124</sup> [http://ec.europa.eu/health/files/paediatrics/2013\\_com443/paediatric\\_report-com\(2013\)443\\_en.pdf](http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf)

<sup>125</sup> Lindell-Osuagwu, L., M. Hakkarainen, et al. (2014). "Prescribing for off-label use and unauthorized medicines in three paediatric wards in Finland, the status before and after the European Union Paediatric Regulation." *J Clin Pharm Ther* 39(2): 144-53.

Dell'Aera, M., A. R. Gasbarro, et al. (2007). "Unlicensed and off-label use of medicines at a neonatology clinic in Italy." *Pharm World Sci* 29(4): 361-7; Lindell-Osuagwu, L., M. J. Korhonen, et al. (2009). "Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature." *J Clin Pharm Ther* 34(3): 277-87. Santos, D. B., A. Clavenna, et al. (2008). "Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil." *Eur J Clin Pharmacol* 64(11): 1111-8.





### 3.4 EU case law

Pursuant to Article 4.3 TEU, Member States are under a duty of sincere cooperation with the European institutions. According to this principle, “*the Union and the Member States shall, in full mutual respect, assist each other in carrying out tasks which flow from the Treaties*”. The article further states that “[*t*]he Member States shall take any appropriate measure, general or particular, to ensure fulfilment of the obligations arising out of the Treaties or resulting from the acts of the institutions of the Union” and that “[*t*]he Member States shall facilitate the achievement of the Union's tasks and refrain from any measure which could jeopardise the attainment of the Union's objectives”.

This principle of Union loyalty has been decisive in capturing the precise scope of the obligations of MS and of several important constitutional principles of EU Law: the duty to give direct effect to directives against the State, the duty of national courts to give effective protection to rights given by EU law, the duty to interpret national law so as to be compatible with EU law, and the right to judicial review. These principles are the foundation of the constitutional structure that the Court of Justice has built and in which national courts ensure the rule of EU law in most of the circumstances in which it applies.<sup>126</sup>

General EU pharmaceutical law supports that prior marketing authorisation is standard. Once this legislation derives from primary law, this obligation should be understood as the most appropriate “default response” to achieve a high level of protection of human health. National and regional entities that perform a public function in the context of pricing and reimbursement of medicines must refrain from undermining this general principle. Therefore, bearing in mind that the marketing authorisation system has been adopted

to ensure the access to safe, effective and high quality medicines for all citizens across the EU, the aim “*to safeguard public health*”<sup>127</sup> must always be included in the evaluation of this restriction-prohibition. Per se, the principle of Union loyalty prevents Member States from broadening the scope of the limited off-label use exception beyond the boundaries accepted or acceptable by European law. This means that off-label use should be considered with regard to **specific medical patient needs**.<sup>128</sup>

In that respect, one should remember that the General Court held in the Pfizer Animal Health case that “**The protection of public health, which the contested regulation is intended to guarantee, must take precedence over economic considerations**.”<sup>129</sup> We submit that the patient safety objectives that the EU system of compulsory marketing authorisations is intended to guarantee must take precedence over purely budgetary considerations put forward to promote the off-label use of certain medicines. Moreover, any such measure should be evaluated on its compliance with the overall public health protection obligation that is imposed on the Member States.<sup>130</sup>

In this line, the CJEU rendered a very interesting judgment in the case *Commission vs. Poland* of 2012.<sup>131</sup> This case concerned a national measure in Poland that provided for a derogation from the requirement for marketing authorisation in the case of medicinal products from abroad which have the same active substances, the same dosage and the same form as medicinal products which have obtained marketing authorisation in Poland, on condition, in particular, that the price of those imported medicinal products was competitive in relation to the price of the products which have obtained such an authorisation. This national restriction was held invalid as a financial criterion cannot justify an exemption from the key elements of Directive 2001/83.<sup>132</sup>

<sup>126</sup> J. Temple Lang, “The Development by the Court of Justice of the Duties of Cooperation of National Authorities and Community Institutions Under Article 10 EC”, *Fordham International Law Journal*, 2007, Vol. 31(5).

<sup>127</sup> Recital 2 of the preamble to Directive 2001/83/EC.

<sup>128</sup> P. Bogaert and A. Schwabl, “Cost considerations should not drive off-label drug use in the EU”, *Scrip Regulatory Affairs*, June 2012.

<sup>129</sup> Case T-13/99, Pfizer Animal Health v. Council [2002] ECR II-3305, paragraph 456.

<sup>130</sup> J. Killick and P. Berghe, “Does promoting off-label use of medicines on budgetary grounds risk jeopardising the integrity of the marketing authorisation requirement system?”, *Pharmaceutical Law Insight*, December 2009, Vol. 6(1).

<sup>131</sup> Case C-185/10, Commission v. Poland [2012] not yet published.

<sup>132</sup> P. Bogaert and A. Schwabl, “Cost considerations should not drive off-label drug use in the EU”, *Scrip Regulatory Affairs*, June 2012.





The CJEU's advocate general stated in his opinion:<sup>133</sup>

*“The aim of Directive 2001/83 is to safeguard public health as well as to ensure that trade is not affected in the market for medicinal products. In my view, the harmonised marketing authorisation procedure is a precondition for access to the market for medicinal products in the European Union, and is the cornerstone of that directive. It enables cost-efficient and non-discriminatory market access, while ensuring that the requirements of safeguarding public health are achieved through meticulous and uniform scrutiny of the pharmaceutical and medicinal properties of the product in question.” (paragraph 19)*

The CJEU confirmed this statement and held:

*“... the possibility of importing non-approved medicinal products, provided for under national legislation implementing the power laid down in that provision, must remain exceptional in order to **preserve the practical effect of the marketing authorisation procedure** ... ” (paragraph 32) and*

*“It is apparent from the conditions as a whole set out in Article 5(1) of Directive 2001/83, read in the light of the fundamental objectives of that directive, and in particular the objective seeking to safeguard public health, that the derogation provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market. **Where medicinal products having the same active substances, the same dosage***

*and the same form as those which the doctor providing treatment considers that he must prescribe to treat his patients are already authorised and available on the national market, there cannot in fact be a question of ‘special needs’, within the meaning of Article 5(1) of Directive 2001/83, necessitating a derogation from the requirement for a marketing authorisation under Article 6(1) of that directive.*

The key principles for the application of article 5(1), as laid down by Commission v Poland could thus be summarized as follows:<sup>134</sup>

- the use must remain exceptional in order to preserve the practical effect of the marketing authorization procedure
- it should only be used when it is necessary, taking into account of the specific needs of patients
- the medicine must be supplied in response to a bona fide unsolicited order, which requires a prescription by a doctor as a result of an actual examination of his patients and on the basis of purely therapeutic considerations
- there is no authorized equivalent medicine available

In the Commission vs. Poland case, the CJEU also held that:

**Financial considerations cannot, in themselves, lead to recognition of the existence of such special needs** capable of justifying the application of the derogation provided for in Article 5(1) of that directive.” (paragraphs 36 to 38). The same reasoning logically applies to any MS rule that directly

*objective of seeking to safeguard public health, that the exception provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that **a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market** (see, to that effect, judgment in Commission v Poland, C-185/10, EU:C:2012:181, paragraphs 29 and 36).” (paragraph 56).*

<sup>133</sup> Case C-185/10, Opinion of Advocate General Jääskinen, Commission v. Poland, 29 September 2011.

<sup>134</sup> It should be noted that the formal requirements of art. 5 (1) may not fulfilled to apply the principles straightforward to off-label use. Whereas art. 5(1) relates to the use of unauthorised products, off-label use concern the use of authorised products but in an unauthorised indication or modality. In that scope the CJEU (Case C-544/14, Abcur AB vs Apoteket Farmaci AB, 16 July 2015) states with regard to art. 5 (1) that :

*“...it is apparent from the conditions as a whole set out in that provision, read in the light of the fundamental objectives of that directive, and in particular the*



permits the non-authorized use of a product for purely financial considerations. It is an infringement of EU law to suspend marketing authorisation requirements for a specific indication of a medicine that is only authorised for something else because they are less expensive than an authorised product. **Measures that stimulate off-label use of medicines cannot be based on purely financial reasons.**

**We must however draw attention to the words “in themselves”. Restrictions based solely on economic reasons are not accepted, but could they be if they are linked to the financial balance of the social security system or the integrity of the national health system?**

In that scope, in the ABPI case, the CJEU stated that:

*“In accordance with Article 168(7) TFEU, European Union law does not detract from the power of the Member States to organise their social security systems and to adopt, in particular, measures intended to govern the consumption of pharmaceutical products in order to promote the financial stability of their health-care insurance schemes”<sup>135</sup>.*

The need to render health care more accessible for the public will not as such be accepted as a valid justification.

In the *De Peijper* case of 1976, the CJEU ruled the following:

*“Health and the life of humans rank first among the property or interests protected by Article 36 and it is for the Member States, within the limits imposed by the Treaty, to decide what degree of protection they intend to assure and in particular how strict the checks to be carried out are to be.*

*National rules or practices do not fall within the exception specified in Article 36 if the health and life of humans can as effectively be protected by measures which do not restrict intra-Community trade so much.*

<sup>135</sup> Case C-62/09, Association of the British Pharmaceutical Industry [2010] ECR I-3603

<sup>136</sup> Case 104/75 De Peijper [1976] ECR 613.

<sup>137</sup> Case C-322/01, Doc Morris [2003] ECR I-14887.

*In particular Article 36 cannot be relied on to justify rules or practices which, even though they are beneficial, contain restrictions **which are explained primarily by a concern to lighten the administration's burden or reduce public expenditure, unless, in the absence of the said rules or practices, this burden or expenditure clearly would exceed the limits of what can reasonably be required**”<sup>136</sup>.*

In the *Doc Morris* case of 2003,<sup>137</sup> the CJEU held that *“Although aims of a purely economic nature cannot justify restricting the fundamental freedom to provide services, it is not impossible that the risks of seriously undermining the financial balance of the social security system may constitute an overriding general interest reason”*. In that regard, it accepted the system of fixed prices for certain prescription medicines.

In the *Asturias* case of 2010,<sup>138</sup> the CJEU accepted the Spanish restriction on the freedom of establishment by limiting the number of new pharmacies that could open in a certain area. The CJEU found that the legislation was justified by the *“objective of ensuring that the provision of medicinal products to the public is reliable and of good quality”*. It followed the reasoning of the Spanish State that there might be a risk that some parts of its territory will be left with too few pharmacies which could have a negative effect on the provision of reliable and qualitative medicines.

It seems to follow from this judgment that restrictive measures are possible to ensure an equal access to medicines of good quality for everyone. However, in doing so, the competent authorities should refrain from circumventing the EU-regulation and undermining the effectiveness of this regulation (*Laboratoires CTRS* case).

Lastly, we need to mention the *Novartis* judgment of 11<sup>th</sup> April 2013 of the CJEU.<sup>139</sup> The case relates to two centrally authorised products, Lucentis and Avastin, which both were used in the EU to treat patients with wet age-related macular degeneration. Only Lucentis however was covered by a marketing authorization for this purpose. Avastin, being the older of the two

<sup>138</sup> Joined Cases C-570/07 and C-571/07, Asturias [2010] ECR I-04629.

<sup>139</sup> Case C-535/11, Novartis v. Apozyt, [2013]: <http://curia.europa.eu/juris/document/document.jsf?text=&docid=136142&pageIndex=0&doclang=en&mode=lst&dir=&occ=first&part=1&cid=571574>.



products, was used to treat AMD 'off-label' before Lucentis became available.

In Germany, Apozyt tried to 'facilitate' the off-label use of Avastin by providing pre-filled syringes. Additionally, it offered pre-filled syringes of Lucentis drawing-off the content from the original vials into several sterile syringes. In doing so the company was able to produce several syringes/injections from one vial, with the respective effect on costs per unit. According to the SmPC only one vial per syringe should be used.

Apozyt was taken to Court by Novartis (the MAH) to stop this activity, based on the argumentation that such modification of the products, could only be done by a marketing authorisation holder.

The CJEU did not follow this argument:

*“(42) In such circumstances, provided that the referring court does in fact find that the processes in question do not result in any modification of the medicinal product and that they are carried out solely on the basis of individual prescriptions making provision for them, there is no ground for considering that the activity thus carried out can be equated with a new placing on the market of a medicinal product included in point 1 of the Annex to Regulation No 726/2004; accordingly, the company concerned is, in that respect, not subject to the obligation to hold a marketing authorisation granted by the Community pursuant to Article 3(1) of the regulation”.*

The CJEU considered that in those circumstances the activity cannot be equated with a new placing on the market. Instead, *“it is in reality analogous to actions which, in the absence of the company's activities, could otherwise be, or have been, carried out, under their responsibility, by doctors prescribing the treatment or by pharmacies themselves in their dispensaries, or else in hospitals”.* However, the CJEU held that Apozyt would be required to hold a manufacturing authorisation.

As to the derogation provided for in Article 5 (1) of Directive 2001/83 the CJEU repeated its earlier case law, but considered that the off-label use of authorised medicinal products may fall under Article 5 of Directive 2001/83/CE by recognizing the therapeutic freedom of a doctor to prescribe an off-label alternative to an available authorised product.

*“(46) It should be borne in mind that Article 5(1) of Directive 2001/83 is a specific derogating provision, which must be interpreted strictly, applicable in exceptional cases where it is appropriate to meet special medical needs, in circumstances in which a doctor, following an actual examination of his patients and on the basis of purely therapeutic considerations, prescribes a medicinal product which does not have a valid marketing authorisation in the European Union and for which there is no authorised equivalent on the national market or which is unavailable on that market (see, to that effect, Case C-185/10 Commission v Poland [2012] ECR, paragraphs 35, 36 and 48). The Court pointed out in particular, in paragraph 37 of that judgment that Article 5(1) cannot be relied on where medicinal products having the same active substances, the same dosage and the same form as those which the doctor providing treatment considers that he must prescribe to treat his patients are already authorised and available on the national market.*

*(47) Thus, in the circumstances of the case before the referring court, that provision cannot be relied on with regard to the use of a medicinal product such as Lucentis, since those circumstances do not entail prescription of a medicinal product different from the product which already has a marketing authorisation; the injection volumes used are no different from those provided for in the marketing authorisation and nor is the product used for a therapeutic indication not covered by the marketing authorisation.*

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



*dosage which he considers appropriate and using Avastin which has a Community marketing authorisation, is preferable to treatment with Lucentis”.*

According to the CJEU, a State can make an authorised medicinal product **available** for therapeutic indications not covered by the MA, if this medicinal product is prescribed by an authorised practitioner **for use by an individual patient under his direct personal responsibility and solely on therapeutic considerations.**

Several of the above mentioned cases illustrate – along with the EU regulations – an increasing attention to the place of health care and public safety considering them as fundamental rights to EU citizens. In this, systems have to deal with the challenge of prioritising health care in a way that balances the needs of individual patients with the financial resources available to treat the whole population. This needs to be interpreted, however, in line with the currently existing EU pharmaceutical regime, which sets the MA as a standard and allows off-label use in limited cases that need to be interpreted in a restrictive way. EU law clearly states that budgetary considerations must not lead national public authorities to promote off-label use and in that jeopardise the integrity of the European pharmaceutical regulatory system. All public authorities have a duty of loyalty towards the EU pharmaceutical regime pursuant to Article 4 TEU, implying that national public authorities must not only positively take all appropriate steps to ensure full implementation of EU law but must also actively refrain from taking measures which could hinder the full implementation of EU law. This precludes the “active support” of certain off-label uses and also precludes the use of off-label rules to manage costs, for which there are specific pricing and reimbursement procedures.

This does not imply, however, that any role for public authorities in the management of off-label use is excluded. As appears from the CJEU jurisprudence, discussed above, a State can make an authorised medicinal product available for therapeutic indications not covered by the MA, if this medicinal product is prescribed by an authorised practitioner for use by an individual patient under his direct personal responsibility and solely on

therapeutic considerations, for which there is no authorised equivalent on the national market or which is unavailable on that market (see principles laid down in the Commission vs. Poland case). An available authorized equivalent needs to be considered as a medicinal product having the same active substances, the same dosage and the same form as the off-label used product and that is already authorised and available on the national market.

It fits in the objective of national authorities to guarantee a high level of protection of health and safety, without unduly interfering in trade relations on the market and the pharmaceutical regulatory framework. In that scope national authorities are competent to ensure that, if off-label products are made available in the individual patient case under the responsibility of the health care professional and in the authorised conditions as mentioned earlier, patient safety and financial accessibility are guaranteed. The communication by national authorities of (available or generated) study results and factual scientific information of the off-label product, without any statement on the recommended use of the off-label application (compared to the use of the licensed product) seems in that respect in conformity with the respective EU legal framework (see also the principles of the Laboratoires CTRS case<sup>140</sup>). Making an authorised product available for off-label use for individual patient cases also implies that reimbursement (see chapter 4 on reimbursement as national competence) for the (evidence-based) off-label use could be foreseen if a healthcare professional decides to prescribe off-label. Actively promoting off-label use because of financial considerations, however, is not in line with the existing EU legal framework.

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<sup>140</sup> According to the Case T-452/14, Laboratoires CTRS vs. Commission, § 78: “(...) off-label prescribing is the sole responsibility of the prescribing physician. That responsibility could in practice be attenuated by the presence,

in a medicinal product’s marketing authorisation, of statements that the product is effective and safe for treating other therapeutic indications than those for which its marketing authorisation has been granted.”





## Key Points

- European law is not intended to impact on the practice of medicine and does distinguish between product regulation and health-care providing. However, national legislation should not undermine the effectiveness of the pharmaceutical regulation.
- Therefore, EU law does not require Member States to prohibit the prescription or administration of medicines outside their authorised indications.
- European legislation enables Member States to exclude from the provisions of the Directive 2001/83 the supply of unlicensed medicines for use by an individual patient, at the order of his doctor and under his direct personal responsibility and solely for therapeutic considerations.
- Public health measures that stimulate or authorize off-label use of medicines cannot be based on purely financial reasons.
- The physician's responsibility to prescribe off-label may not be attenuated by including conclusions in a medicinal product's MA on the safety and efficacy of an off-label indication where an orphan drug having market exclusivity for that indication exist. Member States are free, however, to provide neutral scientific information regarding off-label used products.
- Member States are free to foresee specific reimbursement mechanisms to make off-label products available in individual patient cases under the responsibility of the prescriber.

## 4 SPECIFIC REGULATION ON REIMBURSEMENT

Among the tools put in place by States, **reimbursement of health care is a central element in the promotion and protection of public health**. To that extent, such policies are very much of the **autonomy of the Member States** of the European Union and are largely beyond the control of the bodies of the European Union.<sup>141</sup>

Minimum procedural requirements were however adopted and are contained in the Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems. The recitals of this Directive clearly pose the framework of intervention of the European Union Member States. So read that ***“Member States have adopted measures of an economic nature on the marketing of medicinal products in order to control public health expenditure on such products”*** and that ***“such measures include direct and indirect controls on the prices of medicinal products as a consequence of the inadequacy or absence of competition in the medicinal products market and limitations on the range of products covered by national health insurance systems.”***<sup>142</sup> The next recital states that ***“the primary objective of such measures is the promotion of public health by ensuring the availability of adequate supplies of medicinal products at a reasonable cost; whereas, however, such measures should also be intended to promote efficiency in the production of medicinal products and to encourage research and development into new medicinal products, on which the maintenance of a high level of public health within the Community ultimately depends.”***<sup>143</sup>

<sup>141</sup> ECJ, Case C-245/03 Merck, Sharp & Dohme [2005] ECR I-637, paragraph 27

<sup>142</sup> Second recital to the Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems.

<sup>143</sup> Third recital to the Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems.



In article 1(3) of this Directive, the obligation to respect the marketing authorization system was confirmed: “Nothing in this Directive shall permit the marketing of a proprietary medicinal product in respect of which the marketing authorization has not been issued.”

Once again, regulation is laying the necessary balance between the protection of health and the economic imperatives of enterprises. It is worth noting, in this regard, that the element 'cost' is formally considered an element of access to health.

Moreover, the jurisprudence relating to this Directive confirms that if it did not aim to influence the social policy of the Member States, it raises fundamental formal requirements, such as an obligation of adequate motivation of decisions on reimbursement. In this sense, the Court of Justice held in case C-691/13 (*Les Laboratoires Servier SA v Ministre des Affaires sociales et de la Santé, Ministre de l'Économie et des Finances*) “it would be contrary to the objective of transparency to accept that a decision such as that at issue in the main proceedings may be exempt from the obligation to state reasons provided for in Article 6(2) of Directive 89/105, which seeks to allow interested parties to verify whether decisions relating to the pricing of medicinal products and their inclusion in national health insurance systems are taken on the basis of objective criteria and do not discriminate between national medicinal products and those originating in other Member States.”<sup>144</sup>

Furthermore, in the above mentioned ABPI-case<sup>145</sup>, the Court said that “However, it should be noted that, in order to ensure the effectiveness of Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ 1989 L 40, p. 8), professionals in the pharmaceutical industry, whether or not the prescription of their medicinal products is subject to financial inducements, must also be able to verify that the financial incentive scheme implemented by the public authorities is based on objective criteria and that there is no discrimination between national medicinal products and

those from other Member States (see, to that effect, Case C-229/00 *Commission v Finland* [2003] ECR I-5727, paragraph 39, and A. Menarini *Industrie Farmaceutische Riunite and Others*, paragraph 28).”

Consequently, even though Directive 89/105 has as an underlying principle the idea of minimum interference in the organisation by Member States of their domestic social security policies (Case C-245/03 *Merck, Sharp & Dohme* [2005] ECR I-637, paragraph 27), **national public health authorities which adopt a financial incentive scheme for the prescription of specific named medicinal products are required in particular to make such a scheme public and to make available to health-care professionals and professionals in the pharmaceutical industry the evaluations establishing the therapeutic equivalence of the active substances available belonging to the therapeutic class covered by that scheme.**”

It further appears that this Directive not only applies to individual named products but also to decisions regarding groups of medicines e.g. based on their active ingredient. It follows that if the Directive applies, such schemes are certainly permitted. Reimbursement decisions can therefore perfectly target groups of medicinal products, as defined by a common therapeutic characteristic. In this case, the Court considers that the decision is “a bundle of individual decisions on the inclusion of certain medicinal products in one of the social security schemes.”<sup>146</sup>

- **Health policy, in particular the reimbursement of care, is very largely the autonomy of the States. Reimbursement must first aim the promotion of health.**
- **Nevertheless, European law requires that decisions relating to the reimbursement of medicines are based on objective and verifiable grounds. This applies to both the individual reimbursement and decisions concerning groups of medicinal products, as defined by a common therapeutic characteristic.**

<sup>144</sup> Judgement of the Court (Third Chamber) 26 February 2015.

<sup>145</sup> Case C-62/09, Association of the British Pharmaceutical Industry [2010] ECR I-3603.

<sup>146</sup> Case C-229/00, Commission of the European Communities, v Republic of Finland.





## 5 LIABILITY

European legislation does not intend to regulate the practice of medicine. Therefore, European legislation does not require member states to prohibit the prescription or administration of medicines outside their authorised indications. However, as pointed by the Council in its Conclusions on Common values and principles in European Union Health Systems, six values - which include redress - form the common base of EU health systems.

Indeed, off-label use of medicinal products may raise liability issues. Both product liability (5.1.1) and practitioner's liability (5.1.2) can arise when using; prescribing, promoting or presenting a medicinal product off-label. The possible liability of the pharmacist or the Medical Pharmaceutical Committee can also come into play (5.1.3). Finally, one could raise the question about the liability of a public health authority (5.1.4) when promoting or inducing – even indirectly – off-label use of medicinal products.

### 5.1.1 Product liability

Directive 85/374/EEC on liability for defective products (**Product Liability Directive, PLD**) established the "*principle of strict liability, that is, liability without fault, of the producer for damage caused by a defect in his product.*"<sup>147</sup>

A product will only be considered to be defective if it did not provide the safety that the public at large or an average consumer of the product concerned would expect. L'Ecluse et. al. distinguish four ways products can be defective in: design defects, manufacturing defects, packaging defects and information or instruction defects. For off-label use, the informing of the patient of possible risks is very important. Producers would thus be well advised to mention all possible side effects, including those related to off-

label use in the package leaflet and SmPC, to the extent that these side effects are known.<sup>148</sup>

Even though one cannot totally exclude any liability of the producer of the medicinal product in application of the PLD Directive, when it is off-label used, "*the likelihood of the producer incurring liability under the PLD decreases as the consumer is better informed of a medicinal product's risks*".

A correct information obviously depends on if the producer knew or could/should have known about the off-label use.

The application of the pharmacovigilance rules to off-label used products suggest that off-label use of a medicinal product is a "use to which it could reasonably be expected that the product *would be put within the meaning of Article 6 (1) (b) of the PLD*". *To the extent that this is the case, the product may be considered defective if an adverse reaction occurs in association with off-label use without the producer having warned of this adverse reaction. In principle, the producer will be liable for this defect, unless he can show a ground of exemption for liability*".<sup>149</sup>

When the producer promotes the prescription of a pharmaceutical product for a purpose that has not been authorized (which is prohibited – see 3.2.2), it is clear that the off-label use could be expected.

If the patient's injury results from a (wrong) decision of the physician to prescribe off-label and not from an inherent defect in the pharmaceutical of its SmPC or package leaflet, a producer is unlikely to be held liable.<sup>150</sup>

### 5.1.2 Practitioner's liability

Apart from the producer's liability, off-label use of medicines raises potential liability questions for the prescriber. The **choice of therapy is indeed primarily in the physician's responsibility.**

<sup>147</sup> P. L'Ecluse, C. Longeval and K. T'Syen, "Off label use of medicinal products and product liability", Practical lawCompany – Life Sciences, Multi-jurisdictional guide 2013.

<sup>148</sup> The EMA guidance for pharmaceutical companies on how to prepare and review SmPCs states on this that information on a specific risk observed in off-label use should be provided in section 4.4. of the SmPC when it consists of a serious adverse reaction to which healthcare professionals need to be

alerted.

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000357.jsp&](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000357.jsp&)

<sup>149</sup> Ibid.

<sup>150</sup> P. L'Ecluse, C. Longeval and K. T'Syen, "Off label use of medicinal products and product liability", Practical lawCompany – Life Sciences, Multi-jurisdictional guide 2013.



### 5.1.2.1 No prohibition of off-label prescription

The prescription of medicines for off-label use is not legally forbidden as such.

The fact that medicines are only labelled by public authorities for specific therapeutic indications does not mean that medical practitioners are not authorized to prescribe it outside this "label". The **off-label use of medicines is covered by the legally recognized principle of the therapeutic freedom** (in Belgium, article 11 of Royal Decree nr. 78 of 11 November 1967).

As such, medical practitioners are allowed to prescribe medication for off-label use; however, they must always ascertain that the principles of civil liability and the principles of the patient rights law are not breached, in practice meaning that medical practitioners need to exercise their profession with all reasonable and usual care, skill and forethought.

Off-label use of medicines can serve different objectives and can be supported by different levels of evidence. As to its articulation with clinical research, several elements distinguish between prescribing off-label in an individual patient case and clinical research.<sup>151</sup> The slightest difference isn't that precisely the off-label prescribing in an individual patient case is (in principle) not to aim to grow scientific knowledge but to specifically treat a patient. Off-label use can only be classified as experimental if the intended use was (on top of individual patient treatment) to include it in a clinical trial to generate evidence. In that case, all duties (e.g. patient insurance, advice of an ethical committee) and responsibilities (e.g. no fault liability) related to clinical trials apply.<sup>152</sup> If the off-label use was part of a clinical trial, but prescribed for the treatment of an individual patient, it could qualify as

"innovative therapy" if there is a lack of sufficient knowledge to apply for a marketing authorisation for the drug. Off-label use of (older) products supported by evidence where other incentives result in the non-application for an MA could be classified as routine off-label use.

The assessment of the benefits and the risks of prescribing an off-label medicine should be done case by case. To determine whether off-label use is appropriate or not, the urgency of the patient's situation and the availability of an alternative treatment should be taken into consideration. Depending upon the facts of the particular situation, **off-label use can be justified on the basis of evidence that would be considered inadequate in other contexts when it is the only treatment option for a seriously ill patient. For less seriously ill patients and/or when an "alternative"<sup>153</sup> is available, off-label prescribing should be founded on a stronger basis.** Accordingly, the risk of liability of the prescribing physician will be greater if a suitable licensed alternative is available,<sup>154</sup> and less strong supportive evidence on safety and efficacy is available.

### 5.1.2.2 Off-label prescription constitutive of a "fault"

Medical practitioners will be held liable if three elements are fulfilled: a fault, a damage and a causal relation between the fault and the damage (article 1382 Belgian Civil Code).

It is also commonly accepted under Belgian law that illegal conduct is similar to a fault. However, **since off-label prescription is not forbidden, the prescription as such will not constitute an illegal conduct.**

Prescription of medication for off-label use could be unlawful, however, if this is not done with the usual care, skill and forethought of a medical practitioner in the same circumstances. In that case, the unlawful

<sup>151</sup> I. Vrancken, "Off-label prescription of medication", *European Journal of health law* 22 (2015) 165-186

<sup>152</sup> Law of 7 May 2004 related to experiments to human persons, *B.S./M.B.* 18 May 2004

<sup>153</sup> Referring to an "alternative" does only fit within a specific scope. Where the scope would be the pharmaceutical regulation, an alternative could be an alternative medicinal product. However, an "alternative" could be any other therapy. Even within the pharmaceutical scope, an "alternative" could depend on the quality and adequateness of the compared products. To our opinion,

referring to the existence of an "alternative" is therefore subject to a case-by-case evaluation on the aspect that should be compared by the prescribing practitioner. In that respect, the reference should be made to "available" alternatives, where the availability should also be evaluated on a case-by-case basis.

<sup>154</sup> R. Dresser and J. Frader, "Off-label Prescribing: A Call for Heightened Professional and Government Oversight", *J. Law Med. Ethics* 2009, 476-396, [www.ncbi.nlm.nih.gov/pmc/articles/PMC2836889](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2836889).



prescription of the medicine for unlawful use could be considered as the fault that causally caused the damage within the meaning of article 1382 Belgian Civil Code. On the contrary, **prescription of medication for off-label use is lawful if the off-label use of medication is prescribed with the care, skill and forethought of a medical practitioner in the same circumstances.**

### 5.1.2.3 Interpretation elements

The reference type for the diligent physician, placed within the same external circumstances, is a normative criterion. This means that a physician does not just have the duty of care that is customary among physicians within the same category, but the duty of care of a similar physician, placed within the same circumstances. In other words, Courts have to ask themselves what the same physician in the same circumstances would do.<sup>155</sup>

In assessing this, **three main criteria** will be used by the courts:

- What are the usual practices? Was the prescription of the medication for off-label use in line with the usual practices?
- Is there a scientific basis for the prescription of the off-label medication?
- Informed consent. Did the patient give his informed consent?

#### **Usual practices. The off-label use of medicines is not an exceptional and limited situation**

In order to determine whether a physician has violated his duty of care, courts will apply an objective and heightened standard of care. In particular, courts will consider whether the conduct of the medical practitioner is consistent with the conduct of a reasonable or prudent professional colleague in similar circumstances.

The usual practices of the medical profession is a criterion that can be used by the courts for their assessment; however, courts are by no means bound by them.

In this regard, it is relevant that the prescription of medicines for off-label use is a current practice in the medical sector.

In that perspective, the Belgian advisory committee on Bioethics wrote in its opinion nr. 47 of 9 march 2009 relating to the ethical consequences of the new regulation on compassionate use and medical need programs<sup>156</sup> that the prescription of medication for off-label use is a widespread practice. The Belgian advisory committee noted in particular that off-label use mainly occurs with certain populations, especially children, pregnant women and the very elderly.

In relation to paediatrics for example, this is because only very few drugs are examined in detail for babies and very often the drugs are not available in the adjusted dose. Therefore, should the medical corps have to await the official recognition of indications in all situations, several new treatments, which are sometimes vitally important, would only be accessible after a very long time for those specific populations.

This reality is not limited to the paediatrics. On 21 september 2010, the Dutch "College voor zorgverzekeringen" published his official report on Off-label use of innovative drugs ("*Off-label gebruik van innovatieve geneesmiddelen: perspectief van de zorgverzekering*")<sup>157</sup>. The Dutch college noted that within oncology off-label use of medication is even rated at 50 % of all prescriptions (p. 18).

Moreover, the evaluation of the practitioner's choice will necessarily imply an evaluation of possible alternatives, including alternative treatments, alternative medicinal treatments, and alternatives to a treatment. The practitioner's choice will be supported by availability of suitable alternatives, where availability and suitability are to be evaluated with regard to the patient's need. When a suitable tested and approved alternative is available, prescribing physicians' liability may be at (increased) risk if safety issues arise. If an adverse event arises through the use of that drug, the treating physician would have the burden of proof to demonstrate that its use was

<sup>155</sup> T. Vansweevelt en Filip Dewallens, *Handboek gezondheidsrecht – Volume I – Zorgverleners : statuut en aansprakelijkheid*. Intersentia, Antwerpen, 2014, p. 1321.

<sup>156</sup> Online : [www.health.fgov.be](http://www.health.fgov.be)

<sup>157</sup> Online: <http://www.farmaactueel.nl/beleidsstukken/OffLabel.pdf>



performed as standard of care.<sup>158</sup> The scientific basis (see hereunder) will be central to evaluate this.

### Scientific basis

A second criterion that can be used is whether the medical practitioner had a scientific basis for the specific prescription of medication for off-label use. Indeed, a medical act is only consistent with the conduct of a reasonable or prudent professional colleague if it is scientifically justified.

Therefore, the prescription of medication for off-label use can be scientifically justified by medical guidelines. These medical guidelines can be written down in the law, but in Belgium that is almost never the case. If there are no medical guidelines reaffirming that particular prescription of medication for off-label use, it can also be substantiated by medical literature.<sup>159</sup>

When based on medical guidelines or scientific literature, a practitioner will be considered prudent and careful from that perspective.

### Informed consent

The third criterion that will be used by courts to consider whether the prescription of medication for off-label use was done with the usual care of a medical practitioner in the same circumstances, is whether the patient has given his informed consent.

The informed consent of the patient is dealt with in article 8 of the Act of 22 august 2002. Article 8 provides that a patient has the right to give this informed, prior and free consent for each intervention of the medical practitioner. The consent should be explicit, except when the medical practitioner can reasonably assume the patient's consent from the patient's behaviour.

The fact that the patient has given his/her informed consent to the medical practitioner to prescribe him/her medication for off-label use, can be taken into account by the courts as a factor indicating that the physician acted with

the required care of a medical practitioner in the same circumstances. It is thus of an utmost importance that physicians explain the reasons for prescribing a medicine that is unlicensed or being used outside the scope of its licence. Furthermore, it should also be indicated, where there is little research or other evidence of current practice to support its use, or the use of the medicine is innovative.<sup>160</sup>

Moreover, since the consent should be "informed", when such consent is given, this implies that the practitioner was informed himself, according to the paragraph on the scientific basis above.

#### 5.1.2.4 Conclusion

On this basis, we can conclude that the off-label prescribing of a drug is not strictly forbidden by law. It **can only be considered as a violation of a duty of care** within the meaning of article 1382 Civil Code if it is not consistent with the conduct of a reasonable or prudent professional colleague in similar circumstances. Following criteria can be used by the courts to assess this:

- The usual practices
- The existence of "medical guidelines" or scientific literature that confirm those usual practices
- The informed consent of the patient

In other words, off-label prescribing is not a fault as such, only a prescription inconsistent with the conduct of a reasonable or prudent professional colleague would be a fault.

On the other hand and based on the same principles, **in some circumstances the omission to consider off-label prescription could be considered as a fault.**

<sup>158</sup> Riley JB, Basilius PA (2007) Physicians' liability for off-label prescriptions. *Haematol & Oncol News & Issues* May/June: 24–37

<sup>159</sup> See also Court of Appeal of Brussel 21 September 2010, *Unal/UZ Brussels/Sigma Aldrich*, *Tijdschrift voor Gezondheidsrecht* 2012, 183-189

<sup>160</sup> General Medical Council. Consent: patients and doctors making decisions together, 2008. Available at [http://www.gmc-uk.org/static/documents/content/Consent\\_0510.pdf](http://www.gmc-uk.org/static/documents/content/Consent_0510.pdf)



### 5.1.3 Liability of the pharmacist or the Medical Pharmaceutical Committee

Pharmacist's liability could also come into play in the preparation of off-label used pharmaceuticals or in the advice given to patients. Pharmacists have a professional responsibility to ensure that patients receive medication that is safe, effective, and appropriate for their condition and their circumstances, with minimal risk.<sup>161</sup> This responsibility also fully applies to off-label medication. It may be possible to use another dosage than the one included in the package leaflet or an authorized dosage form via an alternative route of administration, e.g. use of an injection solution by the oral route or the use of oral liquids rectally. In that case a compounded preparation specifically prescribed for a specific patient need to be prepared in a pharmacy under the responsibility of the pharmacist. Compounding preparations includes particular risks.<sup>162</sup> Dividing up doses for instance may create risk of contamination and may imply liability questions.<sup>163</sup> Given the broad definition of a "producer" in the Product Liability legislation, the pharmacist could incur personal liability under this legislation for any product defect.

Pharmacists also have the overall responsibility to properly advise patients on how to use the medication supplied. They have to analyse the prescription with regard to the pharmacological aspects, indications, interactions, possible side effects and other related problems.<sup>164</sup> For off-label used pharmaceuticals, however, a pharmacist will often be unaware that a medicine was prescribed off-label, unless it includes a compounded

preparation. They are able to check whether a pharmaceutical was prescribed off-label if it concerns the patient group, dose and mode of administration, but not the indication. As such, a risk for liability is unlikely if it concerns off-label use they could not have been aware of.

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

The regulations stipulate that the formulary must be compiled in a considered and economically justifiable manner.<sup>165</sup> They do not state however that an MFC must abide by the information in the leaflet for instance. There is room for discussion on the inclusion of similar medicinal products with a partially overlapping list of indications in the formulary. For one, this would be the case already for a number of low molecular weight heparins (a class of anticoagulant medication). This means that if the MFC wants to list all the possible indications in the formulary on-label, several products will have to be included, which may not tie in with the hospital administrator's idea of an optimum policy.

<sup>161</sup> P. L'Ecluse, C. Longeval and K. T'Syen, "Off label use of medicinal products and product liability", Practical law Company – Life Sciences, Multi-jurisdictional guide 2013.

<sup>162</sup> In Lisbon the Hospital Sta. Maria was involved in a trial of a pharmacist and a pharmacist assistant, accused of six crimes against physical integrity by negligence. The accusers in this trial, are 6 people who were totally or partially blinded after July 17 2009 after having received intraocular injections allegedly with Avastin at The hospital of Sancta Maria. In the accusation of the pharmacist and the pharmacist assistant, the Minister of public affairs considered that there was an exchange of drugs which took place due to the failure to follow the duties listed in the instructions booklet. The defence on the other hand, claimed that at the time the blindness occurred there was no instruction manual in place for the cytotoxic production unit and denounced

the lack of inspection and supervision, as well as the lack of human resources in the unit. Finally, they were found not guilty, since there was no established evidence what the origin of the blindness was. <http://www.publico.pt/sociedade/noticia/arquidos-no-caso-de-cegueira-no-santa-maria-absolvidos-1598645> ;

<sup>163</sup> [http://www.dn.pt/inicio/portugal/interior.aspx?content\\_id=3209261](http://www.dn.pt/inicio/portugal/interior.aspx?content_id=3209261) ;  
<sup>164</sup> <http://www.ibtimes.com/five-more-eye-patients-go-blind-after-avastin-injections-308554>

<sup>164</sup> Annex to RD of 21 January 2009 related to assignments for pharmacists, *B.S./M.B.* 30 January 2009

<sup>165</sup> Art. 25§1 Royal Decree of 4 March 1991 laying down the accreditation standards for hospital pharmacies, *B.S./M.B.* 23 March 1991





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

#### 5.1.4 Public health authorities' liability

Under Belgian law, the public authorities' liability is based on similar principles to that applicable to any citizen: **one should prove a fault, a damage and a causal link between the identified fault and the identified damage.**

##### 5.1.4.1 Unlawful or careless policy

A public health policy which is to support, directly or indirectly off-label prescription of drugs also raises the question of the responsibility of the public authorities in case of accident with this therapy. As for any liability issue, promotion of off-label therapies is constitutive of fault in the event that it is either illegal or contrary to the duty of care.

Prudence will analyse the behaviour of a public authority normally prudent and diligent.

As explained above (for the responsibility of care providers) the prescription of drugs off-label is not illegal as such. The question arises from the promotion itself: can one promote off-label use of drugs? According to article 87 of the Community code on medicines, "Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorization has not been granted in accordance with Community law."<sup>166</sup> A policy designed to create off-label prescription of drugs will be illegal if it analyses advertising for the drug (see above). However, in the *ABPI case*<sup>167</sup> the CJEU held that where public authorities need to disseminate **information** about a medicinal product, this shall not analyse as "promotion"

<sup>166</sup> According to the EU-case-law, such promotion could be envisaged provided that it is compliant with the SmPC. Since, however, no information has to be included in the SmPC which is not relevant for the authorized indications, off-label information is unlikely to be found in an SmPC.

of medicinal products; the CJEU held that, as health policy defined by a Member State **does not pursue any commercial aim**, a financial incentive that forms part of such a policy cannot be regarded as commercial promotion. On the other hand, as stated in the *Laboratoires CTRS*-case, by doing so the authorities should not circumvent the applicable regulation and should not undermine the effectiveness of the pharmaceutical regulation.

Therefore, official actions related to off-label use **by the public health authorities will not be illegal as such, if they do not undermine the existing pharmaceutical legal framework.**

Nevertheless, it could constitute a lack of foresight, even if it does not as such undermine the effectiveness of the pharmaceutical regulation. A policy will be considered as a breach of the duty of care, if such behaviour or policy is manifestly unreasonable. In Belgian law, this analysis comes down to the behaviour that a normally conservative authority would not have shown.

- **Off-label use of medicines could raise liability questions for manufacturers (product liability), practitioners, pharmacists and public health authorities.**
- **A producer risks to be held liable if he omitted to warn for possible adverse reactions in association with an off-label use he was aware of or could reasonably have expected or which he actively promoted (which is illegal), unless he can show a ground of exemption for liability.**
- **The application of the pharmacovigilance rules to off-label used products suggest that off-label use of a medicinal product is a "use to which it could reasonably be expected that the product would be put."**

<sup>167</sup> Case C-62/09, Association of the British Pharmaceutical Industry [2010] ECR I-3603.





- If the patient's injury resulted from a physician's (wrong) decision to prescribe off-label rather than from inherent defect in the medicine or in its SmPC/package leaflet, it is unlikely that a producer will be held liable under the PLD.
  - Provided that he obtained the informed consent of the patient, the prescriber can freely decide that off-label use is in the best interests of the individual patient.
  - In some circumstances (e.g. if no alternative treatment was available,..), the omission to consider off-label prescription can be considered as negligence.
  - If the doctor fails to take reasonable care and causes an injury to a patient, he could be sued, in particular for negligence. He could also face criminal charges. The law relating to medical negligence differs across Member States, but generally provides for the imposition of liability on individual prescribers in certain circumstances. A doctor will generally not be considered negligent if his actions would be accepted as proper by a responsible body of medical professional opinion.
  - The three main criteria to evaluate this are: the usual practice, the scientific basis and patient's informed consent.
  - To determine whether off-label use is appropriate or not, the urgency and the gravity of the patient's situation and the availability of an alternative treatment should be taken into consideration.
  - Pharmacists could incur (product) liability if damages occur from a wrongly compounded preparation, prescribed for a specific patient.
  - Pharmacist could also incur liability if they failed to properly inform the patient on the use of the medication supplied. The risk for liability is limited if the pharmacist was unable to be aware of the off-label use (e.g. off-label indication).
- MPCs could incur liability if they exclusively include pharmaceuticals in the formulary because of budgetary considerations. It has to be stressed, however, that the final responsibility to prescribe pharmaceuticals in the individual patient case lies with the physician.
  - The authorities have an overall duty of safeguarding and promoting public health. They remain free to choose the most appropriate way to reach this goal, but they should refrain from circumventing the pharmaceutical regulation.



## 6 LEGAL FRAMEWORK ON A NATIONAL LEVEL

As already explained before, the European legislation does not regulate off-label use of medicinal products in a direct way. As a consequence, MSs have their own rules which differ from each other. In some countries, the matter is regulated by law, in others by good practice guidelines or general professional recommendations and reimbursement decisions.<sup>168</sup> This matter is thus not harmonized.

Moreover, the reasons for regulating or supporting off-label use of medicines can differ from one State to another.

**Special needs of certain patients or groups of patients, for instance in the context of paediatric use, safety, but also the possibility to reduce the cost, which is part of the public health policy, are the main reasons invoked.**

This chapter will analyse the existing systems and underlying justifications on a national level.

### 6.1 Belgium

Belgium does not have specific mechanisms regulating off-label use.

The Law on medicinal products of 25 March 1964 describes different cases where medicinal products may be marketed without or outside the terms of a MA. Article 6*quater* of the Law on medicinal products organises both situations where a product may be prescribed and marketed despite the absence of a relevant MA and situations where such a MA is not required.

Article 6*quater*, § 3 describes and lists the hypotheses where no marketing authorisation is required. Those situations are all situations where a MA would be of no relevance, either because of a non-industrial process (compounded and officinal formulae, radiopharmaceutical products prepared on site, total blood, plasma, human body material, except when an industrial process takes place) or because of the existence of an alternative

protection and authorisation scheme (intermediate products, products used in clinical trials).

Different from those exemption cases, Article 6*quater*, § 1 provides true exceptions hypothesis. In those situations, medicinal products that would require a valid MA can be provided to patients outside the terms of the named or requested marketing authorisation. Those cases are all cases of **unmet medical needs**.

#### 6.1.1 Unmet medical needs exceptions

The first exception relates to a situation where the medicinal product is prescribed in order to respond to **special needs** and provided that the patient cannot be treated adequately with medicines available in Belgium. In that case, the legislator foresees the possibility to prepare those drugs for a group of patients or a single individual patient. This request for preparation shall be done in writing and the prescriber will solely be responsible for this treatment.<sup>169</sup>

A second exception applies to **compassionate use programs** in the sense of Article 83 of Regulation 726/2004/EC.

Compassionate use is described as the provision of non-authorized medicinal products to patients belonging to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. In that case, the medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of Regulation 726/2004/EC or must be undergoing clinical trials.

<sup>168</sup> P. Bogaert and A. Schwabl, "Cost considerations should not drive off-label drug use in the EU", *Scrip Regulatory Affairs*, June 2012..

<sup>169</sup> This provision implements article 5 of the Directive 2001/83.



The third exception is the **medical need program**. This applies to cases where a patient has a chronic disease, a disease with a serious impact or a life threatening disease that cannot be treated satisfactorily by a product that is licensed for this indication (and commercially available) in Belgium. Additional conditions for such provision of unauthorised products are:

- a demand to obtain a MA for the indication in question needs to be in process
- or a MA for the indication has been obtained but the product is not commercially available
- or clinical trials are ongoing on this indication

Both the medical need program and compassionate use program are described in a specific "*Guidance on compassionate use and medical need programs*", edited by the Federal Agency for Medicines and Health Products (FAMHP).<sup>170</sup> This Guidance outlines the criteria and procedures for implementing compassionate use and medical need programs in Belgium. A list of the approved programs is published on the FAMHP website.<sup>171</sup>

Apart from those cases, Article 6*quater*, § 1 allows the **individual import for a named patient** of an unauthorized product from another MS where the product is duly authorized, provided that there is no such authorised product in Belgium or such product is not available, either because the product is not yet on the market or because the MA-holder is out of stock temporarily or on a permanent basis.

Finally, Article 6*quater*, § 1, 5° of the Law on medicinal products of 25 March 1964 allows the Minister of public health or his delegate to authorize the distribution of unauthorized medicines in order to fight against **serious threats for the public health**.

### 6.1.2 Early temporary reimbursement of products targeting an unmet medical need

In 2014 a new law established the process for the early temporary reimbursement of products targeting an unmet medical need.<sup>172</sup> This can be asked for a group of patients (cohort). The aim of the law was to give quicker access to promising, safe and innovative products for unmet medical needs for which no MA has been obtained yet. Cohort decisions are restricted in time and based on available economic and medical data.

Off-label used products can be subject of a cohort decision, if the following conditions are met:

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

<sup>170</sup> FAMHP, Guidance on compassionate use and medical need programs, [www.fagg-afmps.be/en/binaries/UMN%20guidance%202014-09-26-OK\\_tcm292-256000.pdf](http://www.fagg-afmps.be/en/binaries/UMN%20guidance%202014-09-26-OK_tcm292-256000.pdf).

<sup>171</sup> [http://www.fagg-afmps.be/en/human\\_use/medicines/medicines/research\\_development/compassionate\\_use\\_medical\\_need/](http://www.fagg-afmps.be/en/human_use/medicines/medicines/research_development/compassionate_use_medical_need/)

<sup>172</sup> Law of 7 February 2014, *B.S./M.B.* 25 February 2014 and RD of 12 May 2014, *B.S./M.B.* 19 June 2014



Requests for a cohort decision can be submitted by a pharmaceutical company, the Minister of Social Affairs, the Minister of Health and the College of Medical Directors. The Advising Commission for temporary reimbursement assesses whether the product targets an unmet medical need, based on the list of unmet medical needs defined by the General Council of the NIHDI. Requests to put a condition on the list of unmet medical needs can be submitted by the pharmaceutical companies, the College of Medical Directors, the Minister of Health and the Minister of Social Affairs.

The Advising Commission for temporary reimbursement assesses whether the product targets an unmet medical need, based on the list of unmet medical needs defined by the General Council of the NIHDI. It also makes an appraisal of the usual criteria used by the Drug Reimbursement Committee during the regular procedure: the products' added value, its cost-effectiveness, its price, its budget impact, and its place in daily clinical practice.

The cohort decisions of the College of Medical Directors specify:

- the conditions for and level of cost compensation for the product,
- the cohort of patients eligible for early temporary reimbursement (i.e. inclusion- and exclusion criteria) and
- the budget needed for covering the product which is defined yearly.

The agent who submits a request for a cohort decision is responsible for the execution of the programme, the designation of a responsible physician for handling the requests to be included in the programme, administration of a registry of included patients and registration of unexpected adverse events. When the request has been submitted by the Minister of Social Affairs and Health, the NIHDI is responsible for the organization and execution of the programme. After the relevant medicinal product has been authorized, this specific reimbursement scheme may continue until the authorized medicine is duly reimbursed through the standard list-reimbursement applicable for authorized medicinal products.

### 6.1.3 *Off-label use reimbursed by the Special Solidarity Fund*

Individual patients can also ask for reimbursement of their treatment costs by the Special Solidarity Fund (SSF). The main reimbursable categories are the medical treatment costs related to

- Rare indications;
- Rare diseases requiring a specific fysiopathological treatment;
- Rare diseases requiring a continuous and complex treatment;
- Innovative treatment techniques;
- Chronically ill children;
- Medical treatment abroad.

In each of these categories, several eligibility criteria have to be met. Although eligibility criteria are specific per category and need to be applied cumulatively, the following criteria show up in most of the categories:

- The intervention is expensive;
- The disorder threatens the vital functions of the patient;
- The treatment needs to have proven scientific value, effectiveness of the treatment;
- There is no alternative available within the compulsory health system;
- Prescription made by a medical doctor, specialized in the treatment of the related disease.

The SSF has a closed budget and sets a reimbursement basis per individual request. Mostly, the SSF compensates for 75% and 25 % is at the patient's charge, with a maximum of 1250€ per year. It is not clear who covers the costs if the remaining 25% exceeds 1250€/year. If it is not taken into account by the firm, the healthcare provider, the hospital or another party will have to cover these costs.



### 6.1.4 Reimbursement of off-label use in the “regular” reimbursement schemes

The Belgian “regular” reimbursement system – indirectly- provides in some mechanisms to provide financial compensation for off-label used products. The Belgian reimbursement regulation is based on a positive list of reimbursed products. Those products are listed on request of the MAH.

For reimbursement purposes in Belgium, medicinal products are subdivided into a number of classes (A, B, C, Cs, Cx, D, Fa, Fb) and chapters (I, II, III, IV, IVbis, VII) on the list of reimbursable pharmaceutical specialities.<sup>173</sup> For off-label use, an example of a shift from chapter IV to chapter I will be illustrated in the following section.

Medicinal products in **chapter I** were initially solely reimbursed for all the authorised indications listed on the leaflet. Since a 2012 legislative amendment<sup>174</sup>, off-label use now qualifies for reimbursement. Other than for medicinal products in chapter IV, doctors do not have to specify the indication, target group, age etc. So there is no way of knowing whether the contributions the NIHDI pays relate to authorised or off-label use.

The reimbursement of a medicinal product listed in **chapter IV** is governed by conditions that are imposed for medical and/or economic reasons. This entails that reimbursement is limited to e.g. indications, target group, age.... In addition, usually a prior authorisation of the NIHDI advisory physician is required: in general (a number of exceptions excluded) for outpatient care and in clearly specified situations only for hospital use.

Initially, medicinal products listed in chapter I could only be reimbursed for the authorised indication, but following a 2012 amendment to the legislation, their off-label use is now also refunded.<sup>175</sup> Since then, the NIHDI - with the

agreement of the manufacturers and subject to a price reduction to neutralise budgetary consequence due to volume increases - has regularly moved medicinal products listed in chapter IV to chapter I, specifically to facilitate the wider use and reimbursement (than the conditions described in for chapter IV pharmaceuticals) of certain, especially oncology, medicinal products.

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

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

Off-label use **in hospitals** can also qualify for reimbursement. Since 1 July 2006, the acute hospitals have been applying a lump sum reimbursement system per admission for all reimbursable medicinal products, irrespective of their actual use. 25% of the reimbursement basis of the pharmaceuticals covered by this lump sum is still reimbursed per product. However, certain

<sup>173</sup> On the classification see: <http://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/specialiteiten/hoofdstukken/Paginas/default.aspx>; le Polain M, Franken M, Koopmanschap M, Cleemput I. Drug reimbursement systems: international comparison and policy recommendations. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE). 2010. KCE Reports 147C. D/2010/10.273/90https://kce.fgov.be/sites/default/files/page\_documents/KCE\_147C\_Drug\_reimbursement\_systems\_4.pdf

<sup>174</sup> Royal Decree of 12 March 2012 modifying the Royal Decree of 21 December 2001 setting the procedures, terms and conditions related to the financial compensation of pharmaceuticals by the compulsory health insurance, *B.S./M.B.* 19 March 2012

<sup>175</sup> The aim of the amendment was to allow combinations of 2 or 3 pharmaceuticals (in oncology). The combination of on-label pharmaceuticals can result in off-label use (the combination may not be authorised in the label). The amendment indirectly facilitates the compensation of all types of off-label use.





products such as orphan drugs, cytostatics, immunoglobulins, HIV inhibitors... are excluded from this lump sum system.

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

- The medicinal product is reimbursed under chapter I:
  - The medicinal product is charged to the health insurance provider. Since the 2012 legislative amendment, off-label use qualifies for reimbursement.
- The medicinal product is reimbursed under certain conditions (chapter IV):
  - If the medicinal product QUALIFIES for the lump sum system, no prior authorisation from the advisory physician is required (save in exceptional cases): the irrevocable assumption prevails that the reimbursement conditions are satisfied and the chapter I procedure is followed virtually.
  - If the medicinal product does NOT qualify for the lump sum system, only the authorised indications are reimbursed (unless the criteria in chapter IV are even more restrictive). Proof that a medicinal product was used in line with the NIHDI rules is added to the invoice. For some pharmaceuticals the proof does not have to be forwarded but it must be kept at disposal. Where an off-label indication is prescribed, the patient must cover the cost of the medicinal product if it transpires from the hospital's information/justification to the advisory physician that the reimbursement conditions were not met. If the hospital does not notify the advisory physician to that effect, the invoice to the patient can be revoked.

Since 2012, a Category F was created allowing the NIHDI to refund a fixed amount if there are several, often expensive, medicinal products available a (hospital) patient can be treated with. For instance, the health insurance provider could reimburse a fixed amount which may be slightly higher than the price of the cheapest (off-label) medicinal product. If patients do end up

having to take the more expensive medicinal product, because they are unable to tolerate the cheaper product for instance, the difference between the fixed amount and the higher price cannot be passed on to them. In this example, hospitals can use the revenue they generate from using the cheapest product. One application of this reimbursement mechanism for off-label medicinal products is presented in the step-by-step plan (see 8.1.8).

#### 6.1.5 Other funding mechanisms

Beyond the above mentioned reimbursement schemes, other informal opportunities for funding of off-label therapy exist. A possibility would be industry-sponsored off-label use, where pharmaceutical companies would offer price-reductions or free samples of a medicinal product in order to meet actual off-label prescription.

#### 6.1.6 Off-label promotion is banned

Pursuant to Article 9 §1 of Law on medicinal products, it is forbidden to advertise medicinal products for which an MA has not yet been granted. *"Given the very broad statutory definition of "advertising", promotional presentations and discussions of unregistered products at scientific meetings are thus prohibited. However, it is generally assumed that discussing the results of a purely scientific study, such as a clinical trial, at a scientific meeting is allowed provided the purpose is clearly not to boost sales or prescription of the medicine, once registered".*<sup>176</sup>

- **Belgian pharmaceutical law provides several options in which the requirement of a prior marketing authorization may be disregarded.**
- **These are exceptional circumstances which, as such, justify to be interpreted strictly.**
- **These options can be assembled as derogatory situations, namely where an authorisation for placing on the market has no meaning or in cases of unmet medical need.**

<sup>176</sup> <http://www.allenoverly.com/SiteCollectionDocuments/Pharmaceutical%20Advertising%20in%20Belgium.pdf>



- **Common to all those cases is the seek for better treatment of the patient's need – where pharmaceutical product regulation would prevent a patient from an adequate treatment, (broader and higher), health-care regulation would offer the possibility to act outside the product regulation.**
- **Reimbursement of such treatments may be considered for these cases under strict conditions.**
- **Apart from the reimbursement of the formally regulated unmet medical need cases, the Belgian “regular” reimbursement system – sometimes indirectly- provides in some mechanisms to provide financial compensation for off-label used products.**

## 6.2 France

According to Article R.4127-8 of the Public Health Code (PHC), **physicians are free to prescribe the treatment they believe to be the most appropriate within the limits laid down by law and in the light of scientifically proven evidence.** Furthermore this Article states: “*With due regard for this duty of assistance, he must limit prescriptions and medical procedures to what is necessary to ensure high quality, safe and effective treatment. He must weigh up the benefits, drawbacks and consequences of various types of investigation and courses of treatment.*” As such, physicians are allowed to prescribe off-label medicines. However off-label prescriptions should be done in compliance with a temporary authorization for use (TAU) or a temporary recommendation of use (TRU).

**Temporary authorisations of use (TAU)** are issued by the French National Security Agency for Medicines and Health Products (ANSM) and provide early access to new promising treatments for which the benefit-risk ratio is presumed to be positive.

This compassionate use measure is allowed provided that the following characteristics are met:<sup>177</sup>

- Treatment of rare or serious diseases
- No marketing authorisation yet
- No suitable therapeutic alternative in France
- Efficacy and safety are presumed
- Benefit is expected for the patient

There are two types of TAUs: (i) “named-patient TAU” and (ii) the so called “cohort TAU”:<sup>178</sup>

- The “named-patient TAU”:
  - Concerns a single patient, designated by name and who cannot participate in a biomedical research
  - Granted for the duration of the treatment
  - Issued at the request and under the responsibility of the prescribing physician
  - Patients are followed-up, safety and efficacy data are collected according to a protocol for therapeutic use (PTU) (when a PTU is requested by the ANSM)
- The “cohort TAU”
  - Granted for a one-year duration (renewable)
  - Group or sub-group of patients treated and monitored following the criteria defined in a PTU

The **temporary recommendations for use (TRU)** is a special procedure by which a medicine can be authorised beyond its formal marketing authorisation indications and conditions of use (Article L5121-12-1 of the PHC). As long as the benefit-risk balance of doing so is positive – and provides prescription criteria and monitoring procedures for patients whose treatment it covers, a TRU can be issued by the ANSM (Articles R5121-76-1 and following of the PHC). The conditions under which the ANSM may

<sup>177</sup> ICTA Group, “Mangement of ATU and RTU”, [www.icta.fr/expertise/atu-and-rtu.aspx](http://www.icta.fr/expertise/atu-and-rtu.aspx).

<sup>178</sup> ICTA Group, “Mangement of ATU and RTU”, [www.icta.fr/expertise/atu-and-rtu.aspx](http://www.icta.fr/expertise/atu-and-rtu.aspx).



establish such recommendations are specified in a Decree of 30 December 2014.<sup>179</sup>

The TRU 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 a TRU:

- the French Health ministry
- the French Social Security ministry
- the *Haute Autorité de Santé* (Health Technology Assessment agency)
- the *Union nationale des caisses d'assurance maladie* (UNCAM, or the federation of national health insurance funds)
- the *Institut National du Cancer* (INCA, or French cancer institute)
- the Centres of Expertise ("reference centres") in rare diseases
- approved patient associations<sup>180</sup>

Pharmaceutical companies are not eligible for requesting a TRU. However, according to the guideline on "Temporary recommendation for use": "[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.*<sup>181</sup>

Upon the ANSM's request, the pharmaceutical company provides all the information it has on the situation identified by the Agency as potentially falling within the scope of a TRU within three months. This information includes:

- all clinical and non-clinical data for assessing the efficacy and safety of the medicine in question in the identified clinical situation
- the list of ongoing and planned clinical trials (title and objectives) and their progress in France or abroad in the indication of interest, as well as the locations of French investigation centres
- an estimate of the number of French patients that may be affected
- a draft patient monitoring protocol
- a copy of any MA granted in any other country in this indication with the SmPC and the latest Periodic Safety Update Report (PSUR)
- if applicable, a copy of any MA refusal or withdrawal by another country in this indication

For rare diseases and cancer, the ANSM further and simultaneously requests, within the same three-month period, the opinion of the:

- Centres of Expertise ("reference centres") for the rare disease in question, if one exists

<sup>179</sup> Décret n° 2014-1703 du 30 décembre 2014 modifiant les règles relatives à l'élaboration de recommandations temporaires d'utilisation établies en application du I de l'article L. 5121-12-1 du code de la santé publique: [http://www.legifrance.gouv.fr/affichCode.do;jsessionid=616AD3A10EF1B4F7FC56A444CFA6F6.tpdila17v\\_3?idSectionTA=LEGISCTA000025850213&cidTexte=LEGITEXT000006072665&dateTexte=20150901](http://www.legifrance.gouv.fr/affichCode.do;jsessionid=616AD3A10EF1B4F7FC56A444CFA6F6.tpdila17v_3?idSectionTA=LEGISCTA000025850213&cidTexte=LEGITEXT000006072665&dateTexte=20150901);

For more information on the general principles and requirements for issuing a TRU see a guideline published by the ANSM in October 2012; ANSM, Temporary Recommendations for Use: Principles and Information on the Methods Used by the ANSM for Establishment and Implementation. Saint Denis: Agence Nationale de Sécurité du Médicament; 2012, [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/e8daacd4d465d71e95a6333d8af9b461.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/e8daacd4d465d71e95a6333d8af9b461.pdf);

[a6333d8af9b461.pdf](http://www.internationallawoffice.com/newsletters/detail.aspx?q=be954a9b-eb49-4192-9a4f-cde660bc8e9b); C. Picard, "Temporary recommendation for use framework amended", International Law Office, January 2015, [www.internationallawoffice.com/newsletters/detail.aspx?q=be954a9b-eb49-4192-9a4f-cde660bc8e9b](http://www.internationallawoffice.com/newsletters/detail.aspx?q=be954a9b-eb49-4192-9a4f-cde660bc8e9b).

<sup>180</sup> ANSM, Temporary Recommendations for Use: Principles and Information on the Methods Used by the ANSM for Establishment and Implementation. Saint Denis: Agence Nationale de Sécurité du Médicament; 2012, 4, [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/e8daacd4d465d71e95a6333d8af9b461.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/e8daacd4d465d71e95a6333d8af9b461.pdf).

<sup>181</sup> *Ibid.*, 10.



- INCA if the disease in question is a cancer-related one.<sup>182</sup>

Based on the available data and the data gathered from the pharmaceutical company, as well as, if applicable, data from the INCA or centres of reference, the ANSM assesses the assumed risk/benefit ratio of the situation that would lead to a TRU. If the ANSM's assessment determines that the ratio between the **presumed** benefit and the potential adverse effects (or risk) is favourable, the ANSM establishes a draft TRU with an appended patient monitoring protocol and, if necessary, a draft agreement for the involved pharmaceutical company(ies). In case of unfavourable TRU opinion, the party requesting the TRU is informed of this opinion, which is published on the ANSM website.<sup>183</sup>

The MAH is required to implement and fund the collection of data pertaining to the monitoring of patients as described in the procedure (additional testing and consultations related to a patient's standard treatment do not fall within this scope) (see art. L. 5124-8-9). When a medicine is used within the scope of treating a rare disease for which there is a Centre of Expertise, the pharmaceutical company may delegate the patient monitoring, in whole or in part, to this centre.<sup>184</sup>

The pharmaceutical company must fulfil the pharmacovigilance obligations, in particular the requirement to inform the ANSM of any new information that may affect the benefit/risk ratio. The company should also contribute to the good use by ensuring that the medicine is prescribed in compliance with its MA or TRU; when prescriptions that do not comply with such good use are observed, pharmaceutical company must inform the ANSM (see L. 5121-14-3). If there are any emerging health risks, the ANSM can modify, suspend, or even cancel the TRU (see the ANSM principles for TRU).

<sup>182</sup> *Ibid.*, 4-5.

<sup>183</sup> *Ibid.*, 5.

<sup>184</sup> *Ibid.*, 9.

<sup>185</sup> ANSM, Temporary Recommendations for Use: Principles and Information on the Methods Used by the ANSM for Establishment and Implementation. Saint Denis: Agence Nationale de Sécurité du Médicament; 2012, 9, [http://ansm.sante.fr/var/ansm\\_site/storage/original/application/e8daacd4d465d71e95a6333d8af9b461.pdf](http://ansm.sante.fr/var/ansm_site/storage/original/application/e8daacd4d465d71e95a6333d8af9b461.pdf); C. Picard, "Temporary recommendation for use framework amended", International Law Office, January 2015, [www.internationallawoffice.com/newsletters/detail.aspx?q=be954a9b-eb49-4192-9a4f-cde660bc8e9b](http://www.internationallawoffice.com/newsletters/detail.aspx?q=be954a9b-eb49-4192-9a4f-cde660bc8e9b);

Whereas the Health Products Economic Committee (CEPS) has the power to impose financial penalties if the company fails to meet its commitments.<sup>185</sup>

The procedure was originally regarded as an exemption procedure for situations where no therapeutic alternative existed; Article L5121-12-1 of the PHC states that the ANSM may establish a temporary recommendation of use only "**in the absence of appropriate medication alternative with a marketing authorisation**":

*"1. – A medicinal product may be subject to a prescription not in accordance with its marketing authorisation, where there is no suitable alternative medicinal product covered by a marketing authorisation or by a temporary authorisation of use, provided that:*

*1° The concerned indication or conditions of use were the subject of a temporary recommendation for use from the Agence Nationale de Sécurité du Médicament et des Produits de Santé; such recommendation shall not exceed three years;*

*2° Or the prescriber considers that, according to scientifically accepted data, the use of this product is necessary to improve or stabilize the patient clinical condition."*

*(Old Article L. 5121-12-1 PHC, Point I)*

This limit was justified because the TRU was not meant to be a substitute for a MA, the purpose of which is to guarantee a positive benefit-risk balance through approved clinical trials. **If a therapeutic alternative with a MA existed, it had to be chosen.**<sup>186</sup>

<sup>185</sup> [9a4f-cde660bc8e9b](http://ec.europa.eu/health/files/committee/69meeting/pharm614_summary_record.pdf); European Commission, Pharmaceutical Committee, 69<sup>th</sup> meeting, Summary Record, October 2012, 4, [http://ec.europa.eu/health/files/committee/69meeting/pharm614\\_summary\\_record.pdf](http://ec.europa.eu/health/files/committee/69meeting/pharm614_summary_record.pdf)

<sup>186</sup> C. Picard, "Temporary recommendation for use framework amended", *International Law Office*, January 2015, [www.internationallawoffice.com/newsletters/detail.aspx?q=be954a9b-eb49-4192-9a4f-cde660bc8e9b](http://www.internationallawoffice.com/newsletters/detail.aspx?q=be954a9b-eb49-4192-9a4f-cde660bc8e9b); C. Burton, "New French Rules On Off-Label Use", *The national law review*, January 2015, [www.natlawreview.com/article/new-french-rules-label-use](http://www.natlawreview.com/article/new-french-rules-label-use).



In 2013 the legislature made an attempt to create an 'economic TRU' which could be issued by the ANSM "in case of appropriate medication alternative with a marketing authorisation" in order to "avoid expenses with a significant impact on the health insurance finances" (Article L5121-12-1 of the PHC, as amended by the Social Security Financial Law 2013). **This measure never entered into force because an exemption to the principle of marketing authorisation for economic reasons would not comply with EU legislation** (see above: Case C-185/10 Commission v Poland).<sup>187</sup>

On 8 July 2014, the French National Assembly voted a **draft law proposal that would potentially allow healthcare professionals to prescribe off-label drugs, even if there is an approved drug available for treatment.**

The draft law specifically references Avastin, a Roche cancer drug, as an alternative eye treatment for wet age-related macular degeneration, an indication for which the drug is not approved and for which two authorized alternatives exist.<sup>188</sup> During the discussions in the Assemblée, the Minister of Social Affairs and Health also stressed the financial stakes of the issue. (Assemblée nationale, XIVe législature, Session extraordinaire de 2013-2014, Compte rendu intégral Première séance du mercredi 02 juillet 2014). On 6 August 2014 the **Constitutional Court decided that no breach of the constitutional order had occurred.**

The Constitutional Court did not go into a EU law review. The PHC has effectively been modified by law no 2014-892 of 8 August 2014:

*"I. – A medicinal product may be subject to a prescription not in accordance with its marketing authorisation, when there is no medicinal product having the same active substances, the same dosage and the same form covered by a marketing authorisation or by a temporary authorisation of use for the considered indication or conditions of use, provided that a temporary recommendation for use from the Agence Nationale de Sécurité du Médicament et des Produits de Santé secures the use of this product in this indication or these conditions of use and*

*the prescriber considers that the use of this product is necessary to improve or stabilize the patient clinical condition.*

*In the absence of a temporary recommendation for use for the concerned indication or conditions of use, a medicinal product cannot be subject to a prescription that is not in accordance with its marketing authorisation unless there is no suitable alternative medicinal product covered by a marketing authorisation or by a temporary authorisation of use and provided that the prescriber considers that, according to scientifically accepted data, the use of this product is necessary to improve or stabilize the patient clinical condition.*

*II. – The temporary recommendation for use mentioned in I are established for a maximum renewable period of three years. They are made available to prescribers by the holder of the marketing authorisation or by the company that ensures the production of the concerned product"*

*(New Article L. 5121-12-1 PHC, Points I & II)*

Several TRUs have been issued in cases where no suitable alternative medicinal product covered by a marketing authorisation or by a temporary authorisation of use was available, more specifically in the case of Lioresal® and Baclofen® (baclofen), Remicade® (infliximab) and RoACTemra® (tocilizumab).

On September 1<sup>st</sup> 2015, a TRU for the use of Avastin® for AMD came into force for a period of three years. The TRU can be renewed if the safety and efficacy data that need to be registered are favourable. Annual reports summarizing the follow-up of these data will be published in the website of the ANSM.<sup>189</sup>

<sup>187</sup> E. Van Keymeulen, *Making the Patchwork More Transparent: A comparison between national practices regarding off-label use*, March 2014, [www.epaccontrol.com/common/sitemedia/PrePost/PostPDFs/37090.pdf](http://www.epaccontrol.com/common/sitemedia/PrePost/PostPDFs/37090.pdf).

<sup>188</sup> Loi n°2014-892 du 8 août 2014.

<sup>189</sup> <http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/L-ANSM-etablit-la-RTU-d-Avastin-R-bevacizumab-dans-la-degenerescence-maculaire-liee-a-l-age-DMLA-dans-sa-forme-neovasculaire-Point-d-information>





- **France has created a restrictive version of an “authorities solution”: the “temporary recommendations for use” (TRU). A temporary recommendation for use is a special procedure by which a medicine can be authorised beyond its formal marketing authorisation indications and conditions of use.**
- **Originally restricted to situations where there is a lack of therapeutic alternatives, the scheme has been extended now to cases where alternative medicinal products exist, provided that these medicines are not strictly identical.**

### 6.3 Hungary

The basic rules of off-label use are laid down in section 25 of Act No. XCV of 2005, while the specific rules are laid down in Decree No. 44/2004 of the Ministry for Health Care, Social Affairs and Family.<sup>190</sup>

Initially, the prescription and use of a medicinal product for a therapeutic indication other than its authorized indications as specified in the summary of product characteristics was only permitted if

- treatment of the patient with another authorised medicinal product, according to its summary of product characteristics, is not possible or unsuccessful, and based on the experimental evidence defined in specific other legislation, the off-label use of another product offers the potential of a successful treatment, or the improvement or stabilisation of the patient's condition (i);
- the medicinal product in question has been granted a marketing authorization in Hungary or in another (EU or non-EU) country (ii); and
- the physician specialised in the specific therapeutic area has requested individual authorisation from the competent authority (GYEMSZI) for the off-label use of the medicinal product for the specific patient under the relevant conditions set out in specific other legislation, and GYEMSZI

has granted the authorisation. Furthermore, this may only be done if other medication does not make a treatment possible (iii).”

At the end of 2011, another case of off-label prescription was added, which applies if the following conditions are met:

- access to a medicinal product with marketing authorisation for the specific indication is hindered to such a disproportionately great extent that the delay in the commencement of the medical treatment may cause irreversible health impairment to the patient;
- based on the experimental evidence defined in the relevant legislation, administering the medicinal product off-label offers the potential of successful treatment, and/or improvement or stabilization of the patient's condition; and
- the requirements set out in points (ii) and (iii) above are jointly met.

As of 1 January 2013, the legislator further broadened the scope of cases where medicinal products may be prescribed off-label. Now this latter case is amended with the alternative condition of better risk-benefit ratio.<sup>191</sup> Accordingly a medicinal product may also be prescribed off-label if

- the risk-benefit ratio of the medicinal product to be prescribed off-label is more favorable than that of the medicinal product authorized for the therapeutic indication concerned; and
- based on experimental evidence, defined in the relevant legislation, administering the medicinal product off-label offers the potential of successful treatment, and/or improvement or stabilization of the patient's condition; and
- the requirements set out in points (ii) and (iii) above are jointly met.”

Social security reimbursement for the off-label use of a medicinal product may only be granted on an individual basis within the named patient based reimbursement system.<sup>192</sup>

<sup>190</sup> 2012 – Sándor Németh and Róbert Dezso, “Hungary” in Alexander Ehlers and Cord Willhöft (eds.), *Life Sciences in 25 jurisdictions worldwide*, 2012, 49.

<sup>191</sup> 2013 – PMR, “Hungary adjusts its pharma and health related laws to EU regulations”, *Central Europe Pharma News*, 2013, no. 6, 18.

<sup>192</sup> 2015 – Kornélia Nagy-Koppány, László Lencs and Annamária Klára, “Hungary” in *conférence bleue* (ed.), *Pricing and Reimbursement Questions*, 2015, 72-73 & 75.



*"[...] Insured patients – or their treating specialist physicians – may initiate proceedings on a named patient base for the individual reimbursement of a medicinal product not yet admitted into the social security reimbursement system if necessitated by a specific treatment. In this case the National Health Insurance Fund must render the decision on a case-by-case basis depending on the circumstances and costs of the individual treatment and within the limits of the budget of the National Health Insurance Fund. In case of a positive decision, the National Health Insurance Fund will provide assistance for the purchase of the allopathic medicinal product ("Named Based Reimbursement"). [...] Furthermore, the National Health Insurance Fund must also consider comparable technologies which are reimbursed and the reasons why the patient cannot be treated with them. [...]"*

- **The off-label use of any medicinal product is subject to the specific, individual authorization of the Health Technology Assessment Committee and the National Institute for Quality and Organizational Development in Healthcare and Medicines, which is granted upon the request of the patient's treating physician.**
- **Off-label use can be reimbursed on a case-by-case basis by the National Insurance fund. The Health Insurance Fund must render the decision on a case-by-case basis depending on the circumstances and costs of the individual treatment and within the limits of the budget of the National Health Insurance Fund. Comparable technologies which are reimbursed and the reasons why the patient cannot be treated with them must be considered in the assessment.**

## 6.4 Italy

In Italy the use of off-label medicines has been forbidden since 1998. However, **Italian law provides for exceptional conditions in which the off-label use of medicines is allowed and specific cases in which reimbursement is granted as well.**

1. Law Decree no. 536/1996 (converted into Law no. 648/1996) provides in Article 1(4) that, **where no valid therapeutic alternative exists**, medicines can be used "off-label" and are reimbursed by the National Health Service if:
  - the innovative medicines is authorised in other countries, but not in Italy;
  - supporting data deriving from "Phase 2" clinical testing are present;
  - the drugs are inserted in a specific list drawn up and regularly updated by the Italian Medicines Agency (AIFA).The procedures for including a product in the list are listed in the Decision of the Medicines Committee of 20 July 2000. The list of unapproved medicines and off-label use of approved medicines is often referred to as "List 648".<sup>193</sup>
2. Law Decree no. 23/1998 (converted in Law no. 94/1998) provides in Article 3(2) that **doctors, on their own responsibility, can use a medicine "off-label" – including a drug not present in the AIFA list** referred to above – in so far as:
  - the doctor deems that, on the basis of documented data, the patient cannot be successfully treated with a different product, even if said product has been approved for the relevant indication, route of administration or mode of administration;
  - the patient is duly informed and gave his consent;
  - the off-label use is known and consistent with scientific researches published in internationally reputed reviews;

<sup>193</sup> L. Opilio and M.L. Patania, "Italy", Life Sciences In 25 jurisdictions worldwide, 2015, 58, [www.cms-aacs.com/Hubbard.FileSystem/files/Publication/d4086313-7e5a-45e6-9c3f-a0edb2b18515/Presentation/PublicationAttachment/7b946b48-36b6-424d-](http://www.cms-aacs.com/Hubbard.FileSystem/files/Publication/d4086313-7e5a-45e6-9c3f-a0edb2b18515/Presentation/PublicationAttachment/7b946b48-36b6-424d-)

[a156-b028a7a2eaaa/LS2015%20Italy.pdf](http://a156-b028a7a2eaaa/LS2015%20Italy.pdf); P. Bogaert, Non-Compliance of Italian Rules on Off-Label Use of Medicines With the Union Acquis – Complaint in the Context of Article 258 TFEU, January 2015, 9, <http://freepdfhosting.com/18f2b97c63.pdf>.



- supporting data deriving from “Phase 2” clinical testing are present. In this case, the National Health Service shall **not** reimburse the drug.
- 3. In any case, the National Health Service shall not reimburse the off-label use of drugs if such use acquires a regular and widespread character.<sup>194</sup>

In order to reduce the costs for the National Health Service the **rules on off-label use have been amended recently**. Law no. 79 of May 16<sup>th</sup> 2014 inserts a paragraph 4bis in Article 1 of Law Decree nr. 536 of 21 October 1996. The new paragraph amended the existing rules governing the **reimbursement of medicinal products used outside their approved indications** (off-label use) and reads as follows:<sup>195</sup>

*“Even if there is a therapeutic alternative among authorised medicines, following an assessment of the Italian Medicines Agency (AIFA), the medicines that may be used for an indication different from that authorised may be included in the list referred to in paragraph 4, resulting in their supply at the expense of the National Health Service, provided that such indication is known and in conformity with studies carried out within the national and international medical-scientific community, according to cost and suitability criteria. In such a case, AIFA shall establish appropriate monitoring tools to protect the safety of patients and shall promptly adopt the necessary measures.”*

AIFA can now perform **clinical trials on drugs which have not been authorised for a particular use** which, nevertheless, are both cheaper and equivalent to the authorized drug. The trials **aim at inserting non-authorized yet cheaper and equivalent drugs in the AIFA list** referred to above and, as such, be reimbursed by the National Health Service instead of the authorized, more expensive drug.

- **Italy establishes the principle of the prohibition of use of off-label indications. In some cases, however, an off-label use will be permitted and even reimbursed by the social security schemes.**
- **Prior checking (registration on a list) or a scientific validation (choice of physician literature-based) is required.**
- **A widespread use cannot be sufficient to justify a refund.**
- **Before 2014, reimbursement of off-label use was not possible if a valid therapeutic alternative exists. However, since 2014, Italy has introduced a new law allowing the reimbursement of non-authorized yet cheaper and equivalent drugs.**

<sup>194</sup> L. Opilio and M.L. Patania, “Italy”, Life Sciences In 25 jurisdictions worldwide, 2015, 58, [www.cms-aacs.com/Hubbard.FileSystem/files/Publication/d4086313-7e5a-45e6-9c3f-a0edb2b18515/Presentation/PublicationAttachment/7b946b48-36b6-424d-a156-b028a7a2eeaa/LS2015%20Italy.pdf](http://www.cms-aacs.com/Hubbard.FileSystem/files/Publication/d4086313-7e5a-45e6-9c3f-a0edb2b18515/Presentation/PublicationAttachment/7b946b48-36b6-424d-a156-b028a7a2eeaa/LS2015%20Italy.pdf); P. Bogaert, Non-Compliance of Italian Rules on Off-Label Use of Medicines With the Union Acquis – Complaint in the Context of Article 258 TFEU, January 2015, 9-10, <http://freepdfhosting.com/18f2b97c63.pdf>.

<sup>195</sup> P. Bogaert, Non-Compliance of Italian Rules on Off-Label Use of Medicines With the Union Acquis – Complaint in the Context of Article 258 TFEU, January 2015, 9, <http://freepdfhosting.com/18f2b97c63.pdf>; EUCOPE, EFPIA and EUROPABIO, Non-compliance of Italian rules on off-label use of medicines with the union acquis <http://freepdfhosting.com/18f2b97c63.pdf>



## 6.5 Spain

In June 2009 a new Royal Decree has been enacted in Spain in order to speed up procedures and guarantee safety to patients. This new legislation regulates and classifies the availability of medicine use in three special situations: the **compassionate use** of medicines (in the clinical research stage even without being part of a clinical trial), the use of medicines under **conditions other than those authorised** and the use of medicines that are **not authorised in Spain**.

Spanish Royal Decree 1015/2009, regulating the availability of medicines in special situations, defines "off-label" medicines in Article 13.1 as "*drugs used in conditions other than those included in the authorised summary of product characteristics*". The use of medications in such conditions "*shall be exceptional and limited to situations in which there is a lack of authorised alternative treatments for a particular patient*". In addition, "*the doctor must properly justify the need to use the drug in the patient's clinical history and must inform the patient/guardians of the possible benefits and potential risks, obtaining their written consent*".<sup>196</sup>

Under the same Article of the Decree the Spanish Agency for Medicines and Healthcare Products (AEMPS) is entitled to make recommendations concerning off-label use. While making these recommendations, the Agency considers, between other factors, whether the use "*entails a significant health care impact*". In practice, the assessment of the "*health care impact*" comes down to an evaluation of the impact on the public pharmaceutical

expenditure. These health care protocols also establish the possible alternatives for treatment and the order in which they may be used.<sup>197</sup>

Local authorities may impose additional rules. The Catalan Health Service for instance has put internal procedures into place to avoid unwarranted risks and cost of medicines with limited data on their efficacy.<sup>198</sup> This regulation stipulates that the medicine and therapeutics committees of each hospital need to evaluate all cases of medicine use in special situations, and the medical director of each hospital must give individual authorisation for each patient.<sup>199</sup>

- **In 2009, Spain adopted specific legislation concerning off-label drugs. Regulation formally sets out the requirements of necessity (lack of an authorized alternative), a scientific basis and informed consent.**

<sup>196</sup> Royal Decree 1015/2009 of 19 June, on the availability of drugs in special situations is regulated. Official State Bulletin. No. 174 Monday, 20 July 2009. Sec.I. Page 60904 [Document in Spanish] Available at: [www.boe.es/boe/dias/2009/07/20/pdfs/BOE-A-2009-12002.pdf](http://www.boe.es/boe/dias/2009/07/20/pdfs/BOE-A-2009-12002.pdf); Danes *et al.*, "Outcomes of off label drug uses in hospitals: a multicentric prospective study", *Eur.J.Clin.Pharmacol.*, June 2014, 1386, <http://link.springer.com/article/10.1007%2Fs00228-014-1746-2#page-2>; A. García-Sabina *et al.*, "Review of Use of Drugs for Conditions Not Included in Product Characteristics", *Farm Hosp.*, June 2011, 265, [www.aulamedica.es/fh/pdf/ING/318.pdf](http://www.aulamedica.es/fh/pdf/ING/318.pdf).

<sup>197</sup> F. Panetti, *New Frontiers of Pharmaceutical Law – Young Researchers Workshop: a Summary*, May 2010, 9-10, <http://www.opiniojuriscomparatione.org/opinio/article/view/38/42>; Danes *et al.*,

"Outcomes of off label drug uses in hospitals: a multicentric prospective study", *Eur.J.Clin.Pharmacol.*, June 2014, 1386, <http://link.springer.com/article/10.1007%2Fs00228-014-1746-2#page-2>.

<sup>198</sup> CatSalut (2010) Instruction 05/2010. Use of drugs approved under conditions other than those laid down in the technical details. [Document in Catalan] Available at: [www.20.gencat.cat/docs/salut/Minisite/catsalut/Proveidors\\_professionals/normatives\\_instruccions/Documents/Arxius/instruccio\\_05\\_2010.pdf](http://www.20.gencat.cat/docs/salut/Minisite/catsalut/Proveidors_professionals/normatives_instruccions/Documents/Arxius/instruccio_05_2010.pdf).

<sup>199</sup> Danes *et al.*, "Outcomes of off label drug uses in hospitals: a multicentric prospective study", *Eur.J.Clin.Pharmacol.*, June 2014, 1386, <http://link.springer.com/article/10.1007%2Fs00228-014-1746-2#page-2>.



## 6.6 Austria

In Austria an agreement was reached between the Austrian Federal Office for Safety in Health Care / the Austrian Medicines and Medical Devices Agency, the Austrian Society for Anesthesia, Resuscitation and Intensive Care (ÖGARI) and the Austrian Patient Advocacy on the following language regime concerning off-label use.

The term “off-label use” refers to the use of a medicinal product in medical care outside its marketing authorisation. There is no legally binding definition in Austrian law, nor the Austrian Medicinal Product Act. Sometimes article 8 of the Austrian Medicinal Product Act is mentioned in this context, but article 8 addresses the so called “named patient use” (i.e. compassionate use): “§ 8. (1) *Proprietary medicinal products do not require a marketing authorisation, if ...*”<sup>200</sup>

Physicians are free to prescribe the medicines they deem necessary (§ 6 StGB). In case of an emergency, physicians are even obliged to treat their patients in a non-licensed way (i.e. unlicensed use, off-label use and compassionate use) (§ 1306a ABGB). **Off-label use requires, however, increased diligence and an additional obligation to inform patients.** It is the **doctor’s responsibility to justify the medicinal and therapeutic need of off-label use in each individual case.** He needs to demonstrate knowledge of the current standard of care (to the best of his/her knowledge under consideration of the current scientific evidence available) (§ 55 ÄG). Patient information plays a central role hereby. If a patient is not informed, consent has been judged to be missing or invalid and the treatment may be regarded as an unauthorised treatment (§§ 6, 88 und 110 StGB Austria).<sup>201</sup>

**The courts did not restrict the practice of off-label use to life-threatening or otherwise serious diseases.** As such, there is also no necessity for a scientifically valid study to demonstrate a drug’s effectiveness. It is **sufficient for the medicine to be seen as promising**

**by a specialised medical assessment** (Oberster Gerichtshof Österreichs (Austria High Court) decision of 26 March 1996 and 29 April 2003).<sup>202</sup>

All costs of diagnostic procedures and treatment regimes that have been approved for the particular indication or are performed according to published expert recommendations are covered by the federal health insurance. However, in case of off-label use or compassionate use, upon approval by the head physician, the cost of the medicine is reimbursed provided there is no other reasonable current treatment available in Austria that is likely to be successful, or such treatment has been unsuccessful and the off-label treatment has a reasonable probability of success.<sup>203</sup>

- **In Austria, the off-label use is organized on the basis of an agreement between the stakeholders.**
- **The use of such therapy is not prohibited, but relies on greater provider’s responsibility and an obligation to the patient’s informed consent.**
- **A real scientific proof of the efficacy of such treatment is not required, but only the indication of a utility of use.**

<sup>200</sup> Austrian Federal Office for Safety in Health Care, *News Center – Information 16.11.2012*, November 2012, [www.basq.gv.at/en/news-center/news/news-detail/archive/2012/november/16/article/off-label-use/](http://www.basq.gv.at/en/news-center/news/news-detail/archive/2012/november/16/article/off-label-use/).

<sup>201</sup> V. Plate, *The Impact of Off-Label, Compassionate and Unlicensed Use on Health Care Laws in preselected Countries*, 2009, 66 & 84, <http://hss.ulb.uni-bonn.de/2009/1936/1936.pdf>.

<sup>202</sup> Oberster Gerichtshof Österreichs (Austria High Court), Judgment of 29 April 2003 – 10 Obs 409/02y; C. Lenk and G. Duttge, “*Ethical and legal framework and regulation for off-label use: European perspective*”, *Ther.Clin.Risk Manag.*, July 2014, 544, [www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/).

<sup>203</sup> R. Herzig, “Austria”, *Life Sciences in 24 jurisdictions worldwide*, 2014, 13, [www.preslmayr.at/tl\\_files/Publikationen/2014/LS2014%20Austria.pdf](http://www.preslmayr.at/tl_files/Publikationen/2014/LS2014%20Austria.pdf).





## 6.7 Germany

In Germany physicians have the therapeutic freedom to prescribe the medicines that are necessary according to them, even if this comes down to an off-label application of these medicines (§ 1 Abs. 2 BÄO). As in Austria, a physician is even obliged to treat their patients in a non-licensed way in case of an emergency (§ 34 StGB in Germany), as long as he acts according to the current standard of care.<sup>204</sup>

Any medical intervention is considered to contain the elements of the legal offense known as physical injury, as defined by §§ 223 ff. StGB; 823 I BGB. Like any other physical injury, medical interventions can be sanctioned under criminal law. However, interventions into the patient's legal domain are considered to be lawful if the patient has given his consent or presumed consent or in case of a justifying emergency (§ 34 StGB). In case of off-label use, the following considerations apply to the preservation of patients' rights and the medicolegal protection of physicians, according to the highest German court, the Bundesgerichtshof: "***The patient must be informed of the use of a non-approved medication, because, regardless of its actual quality or safety, the medication still lacks the sanction of official approval, which may be essential for an individual patient's decision under the scope of the Medical Preparations Act.***"<sup>205</sup>

By German civil law, MAHs can be held responsible for damages to health, that are found to be not inconsequential and for harm that occurred while the medicine was used as specified. This includes scientifically accepted as well as frequent or typical incorrect uses. The liability of the physician for medical malpractice originates from § 611 BGB (contractual relationship of physician and patient) and the law of torts §§ 823ff BGB. If a patient is killed

or harmed by medication and the responsible pharmacist could have prevented the event, the pharmacist can be found guilty of tortious liability.<sup>206</sup>

In principle, the SGB V (Sozialgesetzbuch) does not allow reimbursement of off-label use by public health insurance companies. However, this principle does not imply that the substance cannot be successfully used or that the patient has no right to request and receive it. In a 2002 ruling the Bundessozialgericht (BSG) made it clear that there are exemptions from this rule and that patients do have the right to receive off-label medicines in case of:<sup>207</sup>

- a serious medical condition;
- no other therapy is available;
- there is good reason to believe that the treatment will be effective.

As a result of the 2002 BSG ruling, Article § 35c(1) of the SGB V, the Federal Ministry of Health is empowered to appoint and commission expert panels "to determine in which cases authorized pharmaceuticals can be used to treat diseases, even though the pharmaceutical has not been authorized for the disease in question [...]."

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. The recommendations of these are forwarded to the Joint Federal Committee of Physicians Dentists, Hospitals, and Health Insurance Funds (GBA). The **GBA 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

<sup>204</sup> V. Plate, *The Impact of Off-Label, Compassionate and Unlicensed Use on Health Care Laws in preselected Countries*, 2009, 66, <http://hss.ulb.uni-bonn.de/2009/1936/1936.pdf>.

<sup>205</sup> NSTZ 1996, 34 [34]; M. Parzeller *et al.*, "Patient Information and Informed Consent before and after Medical Intervention", *Dtsch Arztebl.*, 2007, 1-2, [www.aerzteblatt.de/pdf/DI/104/9/a576e.pdf](http://www.aerzteblatt.de/pdf/DI/104/9/a576e.pdf).

<sup>206</sup> V. Plate, *The Impact of Off-Label, Compassionate and Unlicensed Use on Health Care Laws in preselected Countries*, 2009, 83, <http://hss.ulb.uni-bonn.de/2009/1936/1936.pdf>.

<sup>207</sup> N. Ditsch *et al.*, "Off-label use in Germany – a current appraisal of gynaecologic university departments", *Eur J Med Res.*, January 2011, [www.ncbi.nlm.nih.gov/pmc/articles/PMC3351949/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3351949/); S. Oberman, "Off-Label Use of Medicines – General Aspects, Challenges and Strategies", master thesis, 2013, 16.



of the Pharmaceutical Directive. **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.<sup>208</sup>

If a physician intends to prescribe a medicine for an off-label indication that is not listed in appendix VI of the Pharmaceutical Directive, compassionate use is possible, however, the costs can only be refunded if the three key requirements determined in the above mentioned 2002 BSG ruling are fulfilled:<sup>209</sup>

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

The latter condition applies

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

In 2005 a ruling of the Bundesverfassungsgericht strengthened the grounds for off-label prescribing. According to this ruling, the costs for off-label use should also be refunded if there are only weak references for efficacy, on condition that the patient suffers from a life threatening condition and alternatives are missing. This ruling is based on the fact that the previous

requirements were deemed to be not in compliance with the fundamental rights stipulated in the German Basic Law. Based on a later judgment of the BSG, 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”).<sup>210</sup>

In 2006 the BSG further specified and liberalised the requirements. 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*”. If his demand is declined, he has the possibility to write a private prescription. If a physician does not comply with these provisions, he may be called to pay for the off-label prescription.<sup>211</sup>

- **In Germany, the use of a drug off-label can lead to criminal penalties. Only cases of absolute necessity justify prescribing a drug outside its registered indications.**
- **In Germany, four “off-label expert panels” were established. GBA is responsible for defining which of the assessed pharmaceuticals are “prescribable for unauthorized indications”. Listed indications can be refunded by health insurance companies, provided that the MAH has given informed consent.**

<sup>208</sup> S. Oberman, “Off-Label Use of Medicines – General Aspects, Challenges and Strategies”, master thesis, 2013, 17; Lenk and G. Duttge, “Ethical and legal framework and regulation for off label use: European Perspective”, *The Clin Risk Manag.*, July 2014, 543.

<sup>209</sup> S. Oberman, “Off-Label Use of Medicines – General Aspects, Challenges and Strategies”, master thesis, 2013, 17-18; Decision Resources, Inc., *The SAGE Handbook of Healthcare*, 2008, 69.

<sup>210</sup> *Ibid.*

<sup>211</sup> *Ibid.*



## 6.8 The United Kingdom

In the UK the use of off-label medicines is regulated by the Human Medicines Regulations 2012 which implement Directive 2001/83/EC and Regulation 726/2004/EC.

Under the Human Medicines Regulations, unless an exemption applies, all of a medicinal product's indications must be covered by a valid marketing authorisation (MA) before being supplied for use for the relevant indication in the UK.

The Human Medicines Regulations also implement the so-called “**named patient**” exemption at Article 5(1) of Directive 2001/83/EC, which provides a restrictive **exemption from the obligation for all of a product's indications to be covered by a MA**. This exemption permits the manufacture, import and supply of an unlicensed medicinal product (commonly known as a 'special' in the UK) in response to an unsolicited request from a healthcare professional, provided that the product is for use by an individual patient under the **direct personal responsibility of the requesting healthcare professional** who has concluded that the product is necessary to meet the specific clinical needs of that patient.

Imports of unlicensed products under this regime are subject to a 28-day negative authorisation process operated by the Medicines and Healthcare Products Regulatory Agency (MHRA). According to guidance issued by the MHRA a 'special' may **not** be supplied **if an equivalent licensed product is available** which can meet the special clinical needs of the individual patient. Furthermore it may not include reasons of cost, convenience or operational needs. The use of such unlicensed/off-label products is under the physician's own personal responsibility. The legislation restricts procurement of these products to registered prescribers and pharmacists (or specifically licensed special suppliers).

In practice, decision-making by health professional prescribers, whether or not to use medicines off-label, is generally done in accordance with authoritative clinical guidelines (e.g. NICE) and in line with policies developed and operated by the relevant healthcare providers such as NHS Hospital Trusts, Clinical Commissioning Groups and Health Boards. Such policies generally also provide for patient consenting procedures as a pre-

requisite for **off-label use** and this approach has been broadly endorsed by the UK doctors' regulatory authority, the General Medical Council in its own prescribing guidance. NICE publishes specific guidance documents, i.e. evidence summaries for unlicensed or off-label medicines.<sup>212</sup>

For NHS patients in England (Scotland, Wales and Northern Ireland each operate their own respective regimes) decisions to **fund particular medicines** in primary care are generally made by local Clinical Commissioning Groups ('CCGs') of which there are 212 and which have local budgetary control. These are overseen by NHS England via its Local Area Teams and are allocated a fixed amount of money by the government for the healthcare needs of their local populations. Medicines Management Groups sitting within CCGs draw up local formularies of medicines which the CCG will fund. In some therapeutic areas CCGs have **off-label formularies of medicines, or include off-label uses in their formularies where the CCG has decided to fund off-label use** – usually in therapy areas where there are few authorised products (e.g. for children) or where there is significant clinical authority supporting specific off-label use (e.g. in pain management). In certain therapeutic areas, high cost medicines (e.g. medicines usually prescribed in secondary or tertiary care which are not funded under the Payment by Results tariff) are funded through separate, centrally run streams and procurement and funding decisions are taken at a regional / national level by NHS England or via the Cancer Drug Fund.

In either case, there is some limited scope for funding of off-label medicines not funded under these general funding allocation procedures by applications made through NHS Individual Funding Requests ('IFR') processes. Under these processes a doctor or other health care provider directly involved in the care of a patient, can make an individual request for funding for a treatment for which funding has not otherwise been approved.

As mentioned above, some off-label use of cancer drugs may also be funded centrally through the 'Cancer Drug Fund', a £200 million per year fund which has been set up by the government to enable patients' access to cancer drugs which are not routinely funded by the NHS. The fund is run by NHS England; it was established in 2010 and will run until the end of March 2016.

<sup>212</sup> <http://www.nice.org.uk/advice?type=esuom>



Applications for funding can only be made by a cancer specialist, supported by their hospital trust on behalf of an individual patient or patient group.

In July 2014, days after the French National Assembly backed the above mentioned law concerning off-label, a bill was introduced in the UK to grant licences for **off-patent drugs in new indications**. It aims to make the British government seek new licences for off-patent medicines that could benefit patients whenever pharmaceutical companies fail to do so because there is no financial incentive. The bill requires the Secretary of State to take steps to secure a licence for off-patent drugs in relation to new ways which have been found to use them. It also requires an annual report on the steps taken under its provisions. In this way, the bill intends to reduce off-label prescribing and give generic drug makers other marketable indications for their products. However, contrary to France, **this bill didn't find enough support and is unlikely to progress further**. The Off-patent Drugs Bill remains on the Order Paper of Parliament, should the Government decide to rethink their decision.<sup>213</sup>

- **The United Kingdom is considering the off-label use from several angles (reference to guidelines, instructions etc.).**
- **Decision-making by health professional prescribers, whether or not to use medicines off-label, is generally done in accordance with authoritative clinical guidelines (e.g. NICE) and in line with policies developed and operated by the relevant healthcare providers such as NHS Hospital Trusts, Clinical Commissioning Groups and Health Boards.**
- **NICE publishes specific guidance documents, i.e. evidence summaries for unlicensed or off-label used medicines.**

- **According to guidance issued by the Medicines and Healthcare Products Regulatory Agency a 'special' may not be supplied if an equivalent licensed product is available which can meet the special clinical needs of the individual patient and it does not include reasons of cost, convenience or operational needs.**
- **In some therapeutic areas local Clinical Commissioning Groups have off-label formularies of medicines, or include off-label uses in their formularies where the CCG has decided to fund off-label use – usually in therapy areas where there are few authorised products (e.g. for children) or where there is significant clinical authority supporting specific off-label use (e.g. in pain management).**

## 6.9 The Netherlands

In the Netherlands, Article 68 of the Medicines Act provides that **off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards** with regard to that specific off-label use. If protocols or standards are still in development, the physician and the pharmacist are required to consult.

In addition, the Medicines Evaluation Board (MEB) and the Dutch Healthcare Inspectorate (IGZ) have developed guidelines to distinguish between "correct off-label use" and "incorrect off-label use". **Correct off-label use** is the prescription of a medicinal product for an indication for which scientific evidence exists but which has yet to be assessed by the MEB. Indeed, physicians are sometimes obliged to prescribe medicinal products off-label when no other alternative is available, or they may decide to prescribe off-label if this would be the best possible treatment for the individual patient under the circumstances. However, physicians must remember to inform their patients that the use is off-label and explain the pros and the cons of the treatment. **Incorrect off-label use**, on the other hand, is the prescription of a medicinal product for a non-approved

<sup>213</sup> <http://services.parliament.uk/bills/2014-15/offpatentdrugs.html>; G. MacDonald, "UK Gov should seek licenses for off-patent drugs in new indications says MP", in *PharmaTechnologist*, July 2014, [www.in-pharmatechnologist.com/Regulatory-Safety/MP-UK-should-look-for-off-patent-drugs-in-new-indications](http://www.in-pharmatechnologist.com/Regulatory-Safety/MP-UK-should-look-for-off-patent-drugs-in-new-indications); Breast Cancer Campaign, "Breast Cancer Campaign comments on outcome of

debate in Parliament of the Off-patent Drugs Bill", November 2014, [http://www.breastcancercampaign.org/articles/breast-cancer-campaign-comments-on-outcome-of-debate-in-parliament-of-the-off-patent-drugs#sthash.aYQbj7Ql.dpuf.?&\\_suid=14297032571810013879252957036625](http://www.breastcancercampaign.org/articles/breast-cancer-campaign-comments-on-outcome-of-debate-in-parliament-of-the-off-patent-drugs#sthash.aYQbj7Ql.dpuf.?&_suid=14297032571810013879252957036625)



indication, for which medical or scientific evidence is lacking. Failure to adequately inform the patient that a particular use of a medicinal product has not been approved also constitutes incorrect off-label use.

Off-label use is only permitted if off-label prescription guarantees the best possible treatment for the individual patient. For example, if no medicinal product with MA is available and off-label application is described in the medical literature and guidelines, or if an off-label application has proven to be more effective than the use of medicinal products with marketing authorisation for that specific indication. The **prescribing doctor must have a convincing rationale why off-label use of the medicinal product in that situation is justified**.<sup>214</sup>

Reimbursement of off-label medicines is possible if the off-label use is in accordance with the criteria specified above.

- **In the Netherlands, Article 68 of the Medicines Act provides that off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use. If protocols or standards are still in development, the physician and the pharmacist are required to consult.**
- **According to the Medicines Evaluation Board and the Dutch Healthcare Inspectorate correct off-label use entails the requirements of existing scientific evidence and providing correct information about pros and cons to the patient.**

## 6.10 Switzerland

According to Article 9 of the Swiss Federal Law on medicinal products and medical devices (HMG) ready-to-use medicinal products may only be put on the market if they are authorised. However, there are exemptions to this rule: medicines produced on the basis of a compounded formula, officinal formula or a pharmacist's own formula, medicines intended for clinical trials and medicines which cannot be standardised (Article 9, par. 2). Next to these exemptions Article 9 HMG also includes the possibility for the Swiss Institute of Therapeutic Products (Swissmedic) to "*authorise, for a limited period, the distribution or supply of unauthorized medicinal products against life-threatening diseases if such an authorization is compatible with the protection of health, that a significant therapeutic benefit is expected from the administration of these medicines, and that no equivalent medicine exists" (Article 9, par. 4).<sup>215</sup>*

In practice, five preconditions must be fulfilled to obtain this "special authorisation" (Sonderbewilligung):<sup>216</sup>

1. the disease to be treated had to be fatal or lead to incapacitation,
2. a licensed, acceptable, alternative medicine in Switzerland
  - a. was to be unavailable or
  - b. its risk/benefit-ratios were judged to be poorer or
  - c. it had not achieved satisfying therapeutic results
3. the intervention was to be
  - a. an emergency or
  - b. a last treatment option
4. the medicine
  - a. was found to be licensed in a third party country or
  - b. had a license applied for.

<sup>214</sup> College ter Beoordeling van Geneesmiddelen, [www.cbg-meb.nl/CBG/en/human-medicines/medicinal+products/Off-label/In\\_which\\_cases\\_is\\_off-label\\_prescription\\_permitted/default.htm](http://www.cbg-meb.nl/CBG/en/human-medicines/medicinal+products/Off-label/In_which_cases_is_off-label_prescription_permitted/default.htm).

<sup>215</sup> C. Lenk and G. Duttge, "Ethical and legal framework and regulation for off-label use: European perspective", *Ther.Clin.Risk Manag.*, July 2014, 542, [www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/).

<sup>216</sup> V. Plate, *The Impact of Off-Label, Compassionate and Unlicensed Use on Health Care Laws in preselected Countries*, 2009, 47, <http://hss.ulb.uni-bonn.de/2009/1936/1936.pdf>.



- c. if neither is the case, solid scientific evidence from clinical trials and quality product information on efficacy, safety and quality of the drug was to be presented in the application

5. the medicine was to be used in a single named patient

Additionally, physicians must always respect "*the recognised rules of medical and pharmaceutical sciences*" when prescribing and supplying medicines (Article 26 HMG). These medical and pharmaceutical care duties solidified in a work report made by a think-tank consisting of Swissmedic, the hospital pharmacists, and representatives of the cantons. As such, a medical specialist can only proceed with the therapy if he has obtained the patient's informed consent and has a liability insurance that covers harm that may result from the therapy. He has the obligation to document each case and to issue a report to Swissmedic when a therapy ends.<sup>217</sup>

The requirements for reimbursement of off-label use are difficult to meet. Cost coverage beyond the drugs recorded on a so-called "list of specialties" is possible if there is a scientifically proven "*high therapeutic value*" for cases of life-threatening or chronic disease, and even then only in cases where a "reasonable cost-benefit ratio" exists ("Pompe disease" judgment by the Swiss Federal Court).<sup>218</sup>

- **Switzerland envisages both a system of provisional authorisation for unauthorized drugs and a true off-label. In the first case, the practitioner is requested to meet a demonstrated need and usefulness.**
- **The jurisprudence has led to accept a refund for such treatments.**

<sup>217</sup> C. Lenk and G. Duttge, "Ethical and legal framework and regulation for off-label use: European perspective", *Ther.Clin.Risk Manag.*, July 2014, 542, [www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/); V. Plate, *The Impact of Off-Label, Compassionate and Unlicensed Use on Health Care Laws in preselected Countries*, 2009, 48, <http://hss.ulb.uni-bonn.de/2009/1936/1936.pdf>

<sup>218</sup> C. Lenk and G. Duttge, "Ethical and legal framework and regulation for off-label use: European perspective", *Ther.Clin.Risk Manag.*, July 2014, 544, [www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/).

<sup>219</sup> D. Fairbairn, C. Izzard and M. Holtorf, "Promotion And Use Of Off-label Pharmaceuticals In Europe, The US And China", *Financier Worldwide Magazine*, December 2011, 2, [www.cliffordchance.com/briefings/2012/03/promotion\\_and\\_useoff-labelpharmaceuticalsi.html](http://www.cliffordchance.com/briefings/2012/03/promotion_and_useoff-labelpharmaceuticalsi.html); F. Ma and N. Lou, "Chinese Regulation of Off-label Use of Drugs", *Food & Drug L.J.*, 2013, 193.

## 6.11 China

There are only **limited provisions** related to off-label use of medicines in China. The regulation is scattered among different statutes, national government regulations and local government rules. The right to prescribe off-label remains lightly regulated at the national level. The Ministry of Health has promulgated measures addressing certain aspects of off-label prescribing, but there is no national standard for the practice. However, in addition, there are off-label standards proposed by provinces and hospitals. These include requiring a solid scientific basis for the off-label use, informed consent, and approval of off-label prescribing by a supervising committee.<sup>219</sup>

The Measures for the Regulation of Prescribing, promulgated by the Ministry of Health, contain the only potential source for any prohibition against off-label use. Article 14 of the Measures stipulates that physicians should prescribe drugs based on medical need and medical standards, as well as the indications, pharmacology, dosage forms, strengths, contraindications, warnings and adverse reactions set forth in the drug's approved package insert. As such the legal system in China places a **positive obligation on physicians to prescribe medicines only in accordance with their approved use**. This could be interpreted, in the converse, as a prohibition against off-label prescribing. Such an inference, however, is not supported by the drafting history of the Measures, other related provisions, rules and regulations, and the current system of oversight at the provincial and hospital level. In practice, physicians are at risk of a formal warning, suspension of their practice certificate for between six months to one year, or even the withdrawal of their practice certificate if they have violated these provisions. Comparable rules also apply to pharmacists.<sup>220</sup>

<sup>220</sup> D. Fairbairn, C. Izzard and M. Holtorf, "Promotion And Use Of Off-label Pharmaceuticals In Europe, The US And China", *Financier Worldwide Magazine*, December 2011, 2, [www.cliffordchance.com/briefings/2012/03/promotion\\_and\\_useoff-labelpharmaceuticalsi.html](http://www.cliffordchance.com/briefings/2012/03/promotion_and_useoff-labelpharmaceuticalsi.html); F. Ma and N. Lou, "Chinese Regulation of Off-label Use of Drugs", *Food & Drug L.J.*, 2013, 193.



**Advertisement of off-label use is more clearly prohibited.** To advertise any drug, an enterprise must seek approval from the provincial food and drug administration ("PFDA") of the province, autonomous region or municipality in which the enterprise is located. Any advertisement of a medicine must be conform to its approved product label and insert sheet. The penalties for launching drug advertisements without a permit from the appropriate PFDA can be severe, but there is no criminal prosecution for violators and administrative punishment is generally an insufficient deterrent. Moreover, non-advertisement promotion and non-promotional dissemination of scientific and medical information exist in a grey area that is not regulated by the Chinese government.<sup>221</sup>

**In China off-label use has been permitted** in specific circumstances. One such circumstance occurred during the SARS outbreak in 2004. Certain forms of antibiotic were permitted, even encouraged, by authorities to be prescribed in excess of their permitted dosages specified on the approved product label and insert sheet.<sup>222</sup>

- **China does not directly address off-label use of medicines. Instructions exist, however, to prescribe medicines only in accordance with their approved use.**
- **Off-label use has been permitted in the past, however, in specific circumstances, such as for SARS.**

## 6.12 The USA

Given that the US Food and Drug Administration (FDA) does not have the jurisdiction to regulate the practice of medicine, physicians are free to prescribe FDA approved drugs based on their own medical judgment. They are expected to use their medical judgment, acting in the best interests of the patient, in prescribing medications. **If they are well informed about the product and have a credible clinical justification, physicians may prescribe any drug product approved by the US Food and Drug Administration (FDA), including for off-label uses.** As such they retain their autonomy regardless of whether the prescribed use is included on the drug's label. While doing this, **they stay always subject to malpractice liability.** If the physician's conduct falls outside the standard of care and harms the patient, he can be liable for medical malpractice. In this regard, the fact that a drug use was off-label is not conclusive to establish malpractice liability, however, **evidence of off-label use can be introduced to demonstrate that the physician deviated from the standard of care.**<sup>223</sup>

Despite this "practice of medicine" exception, the federal government has jurisdictional authority to **prohibit drug manufacturers from promoting off-label use.** The Food, Drug, and Cosmetic Act (FDCA) prohibits (1) false or misleading labelling and (2) marketing or promoting off-label uses of medicines to induce commercial sales. The first prohibition of false or misleading labelling is transformed by the agency into an effective prohibition on any advertisement, promotional message, or discussion that is not "consistent with" the approved product labelling, or otherwise

[labelpharmaceuticsi.html](#); F. Ma and N. Lou, "Chinese Regulation of Off-label Use of Drugs", *Food & Drug L.J.*, 2013, 193.

<sup>221</sup> D. Fairbairn, C. Izzard and M. Holtorf, "Promotion And Use Of Off-label Pharmaceuticals In Europe, The US And China", *Financier Worldwide Magazine*, December 2011, 2, [www.cliffordchance.com/briefings/2012/03/promotion\\_and\\_useoff-labelpharmaceuticsi.html](http://www.cliffordchance.com/briefings/2012/03/promotion_and_useoff-labelpharmaceuticsi.html); F. Ma and N. Lou, "Chinese Regulation of Off-label Use of Drugs", *Food & Drug L.J.*, 2013, 195-196.

<sup>222</sup> D. Fairbairn, C. Izzard and M. Holtorf, "Promotion And Use Of Off-label Pharmaceuticals In Europe, The US And China", *Financier Worldwide Magazine*, December 2011, 2,

[www.cliffordchance.com/briefings/2012/03/promotion\\_and\\_useoff-labelpharmaceuticsi.html](http://www.cliffordchance.com/briefings/2012/03/promotion_and_useoff-labelpharmaceuticsi.html).

<sup>223</sup> A. Todd, "No Need for More Regulation: Payors and Their Role in Balancing the Cost and Safety Considerations of Off-Label Prescriptions", *Am. J.L. & Med.*, 2011, 423-424; D. Fairbairn, C. Izzard and M. Holtorf, "Promotion And Use Of Off-label Pharmaceuticals In Europe, The US And China", *Financier Worldwide Magazine*, December 2011, 1, [www.cliffordchance.com/briefings/2012/03/promotion\\_and\\_useoff-labelpharmaceuticsi.html](http://www.cliffordchance.com/briefings/2012/03/promotion_and_useoff-labelpharmaceuticsi.html).



concerns any use that has not been approved explicitly by the FDA, regardless of whether it is truthful or accurately reflects good medical practice. The second prohibition of misbranding is defined as making false or misleading statements in the labelling, or failing to include in the labelling "adequate directions for use". In addition, a pharmaceutical company may also be held liable under the federal False Claims Act (FCA).<sup>224</sup>

The FDA tightly regulates a product's label and the manner in which drugs are promoted. **Off-label cases are vigorously prosecuted in the US.** Pharmaceutical companies have in numerous cases over the past decade paid fines and fees to settle criminal and civil cases of tens or hundreds of millions of dollars, and in some recent notable cases, more than a billion dollars. In 2013, Johnson & Johnson had to pay more than \$2.2 Billion to resolve criminal and civil investigations relating to the prescription drugs Risperdal, Invega and Natrecor, including promotion for uses not approved as safe and effective by the Food and Drug Administration (FDA) and payment of kickbacks to physicians and to the nation's largest long-term care pharmacy provider. The global resolution is one of the largest health care fraud settlements in U.S. history, including criminal fines and forfeiture totalling \$485 million and civil settlements with the federal government and states totalling \$1.72 billion.<sup>225</sup> With the increase in direct-to-consumer marketing by pharmaceutical manufacturers, in 2010 the FDA introduced the Truthful Prescription Drug Advertising and Promotion (Bad Ad) Program. This program provides a mechanism by which health care professionals and patients can report illicit promotion to the FDA. Individual whistleblowers (e.g., current or former employees, competitors, health care professionals) can receive a percentage of penalty as a reward for exposing the off-label usage – sometimes amounting to millions of dollars. In some cases

<sup>224</sup> J. Osborn, "Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information", *Yale J. Health Pol'y L. & Ethics*, 2010, 308-309; D. Fairbairn, C. Izzard and M. Holtorf, "Promotion And Use Of Off-label Pharmaceuticals In Europe, The US And China", *Financier Worldwide Magazine*, December 2011, 1, [www.cliffordchance.com/briefings/2012/03/promotion\\_and\\_useoff-labelpharmaceuticalsi.html](http://www.cliffordchance.com/briefings/2012/03/promotion_and_useoff-labelpharmaceuticalsi.html).

<sup>225</sup> <http://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations>

executives are individual held accountable. They risk prison sentences, exclusion from federal healthcare programs or exclusion from regulatory activities before the FDA.<sup>226</sup>

On August 7, 2015, the U.S. District Court for the Southern District of New York decided that the **prohibition that is held by the FDA to promote off-label use of medicinal products by the marketing authorization holder is contrary to the constitutional freedom of speech.**<sup>227</sup>

As mentioned earlier, the FDA has a long-lasting tradition to consider off-label promotion by the MA-holder as unlawful. However, the MA-holder claimed that he should be entitled to inform health-care professionals on the scientific elements relating to his product, including the fact that there is evidence, however not sufficient, that a product might be effective for the treatment of some diseases.

The district court decided that FDA could not prevent the MA-holder to use his freedom of speech and, thus, to inform truthfully and non-misleadingly about off-label use. However, this does not prevent the FDA from prosecuting a firm that would make not truthful or misleading information.

This judgment is a preliminary ruling and could still be challenged by the US authorities. However, it raises questions about the specific role and boundaries of healthcare regulation.

Regardless of the possible extension to the European situation – where public intervention is much more common – this ruling would confirm that informational communication on off-label use could be considered outside the scope of drug promotion. In evaluating the public authorities' liability, such

<sup>226</sup> C. Wittich, C. Burkle, W. Lanier, "Ten Common Questions (and Their Answers) About Off-label Drug Use", *Mayo Clin Proc.*, October 2012, [www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/); D. Fairbairn, C. Izzard and M. Holtorf, "Promotion And Use Of Off-label Pharmaceuticals In Europe, The US And China", *Financier Worldwide Magazine*, December 2011, 1-2, [www.cliffordchance.com/briefings/2012/03/promotion\\_and\\_useoff-labelpharmaceuticalsi.html](http://www.cliffordchance.com/briefings/2012/03/promotion_and_useoff-labelpharmaceuticalsi.html).

<sup>227</sup> Case *Amarin vs. FDA* available on <http://www.fdalawblog.net/Amarin%20Decision%208-2015%20Off-Label.pdf>



reasoning could certainly be developed and used in courts, especially where this information would be meant to promote public health.

On February 4, 2015, the FDA released a **draft guidance to facilitate streamlining the individual patient expanded access application process**. The Individual Expanded Access Applications: Form FDA 3926. Draft form FDA 3926 proposed by the FDA is a greatly simplified process for doctors to obtain experimental drugs for patients who are suffering from serious or life threatening illnesses and have no other alternative. The FDA has released this document for a 60 day comment from the public, meanwhile the FDA says it won't turn away doctors who want to use it. Patients will be eligible only when there is no other product that can diagnose, monitor or treat the patient's disease or condition and the patient cannot be enrolled in a clinical study testing it and cannot ask the manufacturer or the insurer to pay for the medication. Additionally, the doctor must determine that the probable risk from the experimental drug is not greater than the probable risk from the disease and must ensure that the manufacturer is willing to provide it. This "right to try" law, according to the FDA will give terminally ill patients the right to try experimental drugs that have passed at least the first of three phases of FDA testing (to determine safety) but have not obtained marketing authorisation yet. Some critics of this law believe that providing these drugs prematurely may not be effective since the FDA has more information about potential risks and benefits of drugs under development than a doctor or patient is apt to know.<sup>228</sup>

The Centers for Medicaid and Medicare Services use compendia listings that practitioners use daily to justify the use of off-label drugs for specific diagnoses, e.g. anticancer chemotherapeutic regimen.<sup>229</sup> If an off-label indication is listed in any of the compendia as being supported at a given level of evidence and is not defined by any one of the compendia as being useless, an oncologic drug should be covered for that indication. If a particular indication is supported by studies published in high quality peer reviewed journals, then coverage can also be allowed.

- **In the US, the medical prescription - including off-label - is the freedom and the responsibility of the physician.**
- **Industry promotion for non-registered indications are penalized in terms of misleading advertising. The US has implemented an active policy of prosecution for this. On August 7, 2015, however, the U.S. District Court for the Southern District of New York decided that FDA could not prevent the MA-holder to use his freedom of speech and, thus, to inform truthfully and non-misleadingly about off-label use.**
- **The Centers for Medicaid and Medicare Services use compendia listings that practitioners use daily to justify the use of off-label drugs for specific diagnoses, e.g. anticancer chemotherapeutic regimen.**

<sup>228</sup> <http://www.orpha.net/actor/EuropaNews/2015/150228.html#48647>

<sup>229</sup> <http://www.cms.gov/Medicare/Coverage/CoverageGenInfo/compendia.html>;  
John V. Cox, DO, MBA, FACP, FASCO. Off-Label. 06 Apr 2011 5:56 PM  
<http://connection.asco.org/Commentary/Article/id/2870/Off-Label.aspx>



### 6.13 Conclusion on off-label use in a selection of countries

There is no general rule on formal regulation of off-label use. However, some common trends can be identified in the different legal systems.

All named jurisdictions **exclude** in principle any **advertisement for unauthorized medicinal products**.

**In some cases, the authorities will either directly or indirectly support the use and delivery of unauthorized products, but for the EU Member States concerned, the conformity with EU law has not yet been tested.**

This support occurs through publication of guidelines, reimbursement of off-label used medicines, public funding of health-care institutions that induce a cost-effective prescription schemes.

In some countries, the use of off-label medicines is regulated by law, in others by good practice guidelines or general professional recommendations and reimbursement decisions.<sup>230</sup>

Off-label use is always seen as non-standard measure, meant to complete an overall offer of services and treatments. However, **life-threatening or absolute need is not consistently formally requested**. An **evaluation of the medical need is, however, common** to all named countries.

In line with the common principles identified by the Council, the off-label use can be envisaged by taking into account the need to **treat a patient in accordance with scientific evidence and ethical principles, subject to its consent**. The establishment of scientific standards will be, according to the States, more or less formalized from the scientific consensus that everyone can rely on to the establishment of official expert groups.<sup>231</sup>

Although the off-label use is widespread in cases where no therapeutic alternative exists, the acceptance of such practices, varies from one country to another. The starting point is the patient - or group of patients - with a medical need that is not adequately met by the authorized medicinal products. Some countries, however, implemented mechanisms promoting off-label use for cost considerations (where an alternative exists) as well.

The recent initiatives in Italy, Hungary and France have not yet tested as to conformity with EU law. They do not form evidence of what is possible under EU law. The application of these legal points to off-label use has not yet been directly reviewed by the Court of Justice and the precise nuances may remain unclear for the moment.

- **The practice of off-label use is widespread. Nevertheless, there is no unity in off-label policies in the analysed countries. On the other hand, commercial advertising for such uses is prohibited in a systematic way.**
- **All countries have their own standards for off-label use.**
- **The common element is the need to document or scientifically justify the use of off-label drugs and the need to properly inform the patient.**

<sup>230</sup> S. Oberman, "Off-Label Use of Medicines – General Aspects, Challenges and Strategies", master thesis, 2013, p.13

<sup>231</sup> C. Lenk and G. Duttge, "Ethical and legal framework and regulation for off-label use: European perspective", *Ther.Clin.Risk Manag.*, July 2014, 544, [www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103928/).





Table 1 – Overview of national measures

National measure	Compliance measure	Compliant?
<b>Special need</b>	<ul style="list-style-type: none"> <li>• Only when authorised drugs are not available</li> <li>• Under supervision and responsibility of a healthcare professional, (based, namely on <u>informed</u> consent of the patient)</li> <li>• Request in writing</li> </ul>	Yes
<b>Compassionate use</b>	<ul style="list-style-type: none"> <li>• Chronically or seriously debilitating disease / life-threatening disease</li> <li>• No satisfactory authorised medicinal product</li> <li>• Safety consideration through marketing authorisation application or ongoing clinical trial</li> <li>• Informed patient's consent</li> </ul>	Yes
<b>Medical need program</b>	<ul style="list-style-type: none"> <li>• Chronical disease, disease with serious impact or life-threatening disease</li> <li>• Authorised product available, but not for this indication</li> <li>• Demand in progress</li> <li>• Informed patient's consent</li> </ul>	Yes
<b>Reimbursement art. 25quater/1 Belgian law</b>	<ul style="list-style-type: none"> <li>• Strictly limited to hypothesis where no other <u>treatment</u> is available</li> </ul>	Yes
<b>Expert committee</b>	<ul style="list-style-type: none"> <li>• No suitable alternative</li> <li>• Previous recommendation by authorities or evaluation by prescriber</li> <li>• Very strict rules and intervention of the company</li> <li>• Informed patient's consent</li> </ul>	Yes
<b>Public authorities authorisation</b>	<ul style="list-style-type: none"> <li>• Serious threat for public health</li> <li>• No alternative (except France and Italy – see below)</li> <li>• Authorities are responsible</li> </ul>	Yes
<b>TRU (France)</b>	<ul style="list-style-type: none"> <li>• No suitable alternative (with the same active substance, dosage and pharmaceutical form) as well as when alternative is available</li> <li>• Previous recommendation by authorities</li> <li>• Evaluation by prescriber (based, namely on <u>informed</u> consent of the patient)</li> </ul>	<i>No formal decision on compliance with EU law Inspired by CJEU Commission v Poland (Case C-185/10)</i>
<b>Italy</b>	<ul style="list-style-type: none"> <li>• Use + reimbursement allowed when alternative is available</li> </ul>	No formal decision on compliance with EU law



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	<ul style="list-style-type: none"><li>• Indication is known and in conformity with studies carried out within the national and international medical-scientific community, according to cost and suitability criteria.</li><li>• AIFA shall establish appropriate monitoring tools to protect the safety of patients and shall promptly adopt the necessary measures</li></ul>	
<b>Off-label autonomous prescription</b>	<ul style="list-style-type: none"><li>• Doctors deems that patient cannot be successfully treated with available registered drugs/treatment</li><li>• Own responsibility</li><li>• Scientific evidence</li><li>• Ongoing clinical trial</li><li>• Informed patient's consent</li></ul>	Yes
<b>Named patient</b>	<ul style="list-style-type: none"><li>• Limited to one patient</li><li>• Scientific evidence</li><li>• Informed patient's consent</li></ul>	Yes

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## 7 EXISTING AND PROPOSED MEASURES FOR MANAGED OFF-LABEL USE

### 7.1 Existing measures for parties involved

It appears that several rules exist and that numerous measures have already been taken in different jurisdictions to manage off-label use. In the following sections an evaluation of the existing (European as well as Belgian) principles and measures and proposals for future options to manage off-label use are discussed.

#### 7.1.1 *Incentives to stimulate licensing of off-label use seem to be insufficient*

It appears from this report that all off-label use of drugs schemes are based on common principles. Given the constant search in the various public health policies for protection of human health, the off-label prescription and use of drugs is justified by the balance that must necessarily be found between the formalism of the procedures for authorisation of medicinal products involving a priori validation of efficacy and safety of a product and the need not to waive possible treatments. The central element for the use of a drug outside authorised indications is the scientific validation of the use of exceptional treatments.

In this regard, it cannot be ignored that the off-label use of drugs is a proven and widespread medical reality. As such, it is thus not abnormal or unwise that a health care professional uses a treatment or drug outside the authorised indications. In some circumstances, off-label prescription is the sole option to treat a patient. As such, not considering the off-label prescription would be inappropriate medical behaviour of the health care professional. This is confirmed by the fact that several countries provide a possibility to reimburse off-label prescribed drugs.

Off-label use should be based on the prior existence of sufficient scientific evidence on safety and efficiency to justify such use. This availability of 'evidence' and the fact that it is sound enough will be a case by case assessment, depending a.o. on the context (e.g. common or orphan disease) and the political and legal culture of the various States. Despite the available (indications of) evidence, however, the MAH will often not (yet)

have requested or obtained an extension of his MA for this "new" indication or modality of use. This is also a part of his freedom as undertaking or of the limited rights he acquired on the product.

In many cases, the off-label use of drugs will be induced by the cumbersome procedures and duration of the procedures for registration of drugs and new indications. In this regard, it is interesting to note that incentives are introduced both at the level of the European Union and at the level of different Member States in order to stimulate licensing of new indications for existing medicinal products, for example, the extended protection of data exclusivity (see 3.3.2.1). However, in practice, these measures do not seem to significantly reduce the off-label use.

#### 7.1.2 *Freedom of the prescriber to prescribe off-label, but are prescribers sufficiently informed on the scientific basis?*

It is commonly found that if scientific evidence exists, **a proposal to prescribe an off-label drug falls within the prescriber's freedom**. The general requirement is that of **informed consent** of the patient, which implies that he/she is duly informed of the situation (the fact that the drug is prescribed off-label, the scientific reasons which justify such a choice, the risks that are inherent to that therapeutic choice and the consequences of such off-label use (e.g. a potential non-reimbursement)). Physician-prescribers, like researchers, see their activity widely framed by the rules that exist today. The prescription of drugs outside their registered indication requires to assess the need of this treatment. In this regard the need for treatment will be measured by reference to existing treatments: an analysis of the proportionality of the choice is central. A central difficulty in this regard lies in the reality of the knowledge and real understanding of the elements to be taken into account to make this analysis; the evolution of techniques and medical science could result in unreasonable off-label prescription. Again, the evaluation of reasonableness can be done in terms of the extent of the information given to the patient, based on the information that is available to the prescriber. To that extent, **having published qualitative guidelines will facilitate access to off-label use and reduce practitioners' liability**. It is also of utmost importance to keep an up to date unique patient record that reports precisely each prescription and dispense of medicines as well as patients' reactions after treatment.



### 7.1.3 *Freedom of researchers to perform studies on off-label used drugs, but barriers to confirm successful studies with MA*

Regarding researchers, **continuing studies on drugs registered outside the authorized modality is clearly allowed**. The researcher will ensure in this respect to comply with standards related to medical research and, particularly, the rules governing clinical research. In this regard, one should think in particular to the need to pre-assess the risks associated with the research (e.g. adverse events, absence of effectiveness,...). The need for **patients' informed consent** is primordial in this. Such informed consent **will necessarily involve that the investigator himself is previously adequately informed of risks and benefits** of the option he wishes to test. There again, the existing rules in terms of responsibility and organisation of clinical research are likely to respond usefully to the situation.<sup>232</sup>

A third party could in principle obtain a MA, provided that he would fulfill all legal requirements linked to such application for authorization. In practice, however, the third party may have no access to the active ingredient or on details on the production process because the producer refuses to provide it (mainly based on its intellectual property rights) and/or it may be too expensive for a third party to buy the product to conduct the necessary tests.

### 7.1.4 *Rules for illegal promotion by firms*

**If companies actively promote the use of a drug outside its indications, this could enter the field of prohibited advertisements and will therefore constitute misconduct per se**. It therefore seems unnecessary to further regulate this activity, which is already covered by the current regulations.

Market exclusivity for new drugs is only granted for approved use(s). As such, manufacturers can also make profits from their monopoly with off-label prescriptions. Currently, it is hardly possible to track sales for off-label use. Yet, benefiting from these sales and/or participating in the development of new knowledge without so far actively inciting an off-label prescription, is not illegal as such. The producer's behaviour will be governed by the ordinary law of civil liability: illegal or reckless behaviour will result in the liability of

the producer. Furthermore is still a risk for product liability if the off-label use was reasonably foreseeable (see also 5.1.1).

The existence of the current rules should thus allow the reasoned and balanced approach that puts forward the protection, by the public authorities, of human health.

### 7.1.5 *Existing reimbursement or cost compensation options for off-label used pharmaceuticals*

Compassionate use and medical need programmes were established to give approval for the **use** of promising pharmaceuticals for chronic, serious or life-threatening diseases under specific conditions. The use of pharmaceuticals via these programs can be financially compensated via the (Belgian) existing unmet medical need program.

At the moment of writing this report, it is too early to evaluate the impact of this system. It is not yet known, for instance, how the level of reimbursement will be set. As, by definition, there is no appropriate reimbursed alternative available, price comparison is impossible. If the cost compensation in the cohort decision risks to be way lower than the price of the product in the on-label indication, this may be an incentive for the pharmaceutical firm not to submit a request for a cohort decision. As the off-label use is currently not transparent, firms can benefit from the on-label price for the off-label use. Furthermore, the (lower) price for the off-label indication in the cohort decision could be a basis for price negotiation of the product after the cohort decision period. Finally, the lower price could also be a means of putting pressure on the firm to lower the price of the on-label indication(s).

A company might also be reluctant to engage in such a programme for reasons that are not inherent to the program. If the dose required in the new indication (e.g. in oncology) is a multiple of the dose in the indication for which a MA was obtained (e.g. a non-oncological indication) without a correspondingly higher incremental effectiveness, the company could fear that the very high price of the drug in oncology could bring the overall drug pricing under pressure.

<sup>232</sup> Law of 7 May 2004 related to experiments to human persons, *B.S./M.B.* 18 May 2004



**Cohort decisions within the unmet medical needs program necessarily are initiated by the pharmaceutical firms or include at least their collaboration**, even though the Minister of Social Affairs and Health and the College of Medical Directors are allowed to submit a request for a cohort decision. To be subject of a cohort decision, the respective pharmaceutical needs to be included in a programme for compassionate use or medical need. These programs necessarily imply the initiative or at least the involvement of the pharmaceutical company. **As such, the existing mechanisms do not seem to offer a solution when pharmaceutical firms are unwilling to take the initiative or to collaborate.**

Manufacturers may have several reasons not to take part in a compassionate use or medical need programme.

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

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

The financial compensation of the SSF can also be a restraining factor for firms to apply for a compassionate use or medical need program. If the SSF already compensates the pharmaceutical, the firm may no longer have an incentive to provide the product for free in a program and to wait for a possible reimbursement decision in the unmet medical need program.

An evaluation of the existing programmes therefore seems warranted if they are to be optimally applied.

**Individual patients** can ask for reimbursement of their treatment costs by the Special Solidarity Fund (SSF). The main reimbursable categories are the medical treatment costs related to

- Rare indications;
- Rare diseases requiring a specific fysiopathological treatment;
- Rare diseases requiring a continuous and complex treatment;

- Innovative treatment techniques;
- Chronically ill children;
- Medical treatment abroad.

In each of these categories, several eligibility criteria have to be met.

There are no specific requirements for the quality of evidence that needs to be submitted to evaluate a request for financial compensation. In contrast to the medical need and compassionate use programs there is no requirement that a clinical trial or a request for a MA must be ongoing. Furthermore, it is not required to generate additional evidence or to follow-up the evidence. As such, it is possible that the SSF grants compensation for years without having a long term evaluation of the use of the pharmaceutical. The unmet medical need program, that is integrated in the SSF aims to come forward to these problems.

From a societal perspective, an off-label used product can be desirable if it can substantially reduce disease-related public expenditures, without jeopardizing the outcomes for the patient. This is the case, for instance, when an effective authorized pharmaceutical is available but at a much higher cost than an equally safe and effective cheaper alternative. Today, however, products that are used off-label for such a "societal" need cannot benefit from any cost compensation/reimbursement from the NIHDl via the unmet medical need program nor by the Special Solidarity Fund, since the application of these systems exclude the existence of a satisfactory available alternative within the compulsory health system. The reimbursement of off-label used products where alternatives exist is, however, possible for due to amendments to legislation in 2012 (see 6.1.4). However, this system may not have such an effect as to circumvent the EU pharmaceutical regulation. As such it may solely be applied for therapeutic considerations in the individual patient case under the responsibility of the healthcare professional and not solely for financial considerations. It should also be noted that the current system does not include any systematic (a priori or long term) evaluation of the off-label use.





## 7.2 Possible future measures

The existing off-label use framework shows that there is a need for a clear-cut guidance to manage proper off-label use. **A trend towards governmental management of off-label use can be observed in some countries** (cfr. Chapter 6).

In the following sections, the feasibility of several possible government-supported health promotion measures framing off-label use is discussed. One should remark that **none of these measures stand alone. They should be considered in the overall context of national drug pricing mechanisms, manufacturers' business strategies and patients' and physicians' perspectives to offer a structural solution to off-label use.**

### 7.2.1 Forcing MAH to apply for MA or granting the right to apply for MA to third party only possible if necessary and proportionate

**Forcing a MAH to extend his MA seems to us, as a general rule, not possible.** Obtaining a MA is, indeed, part of its freedom. In some particular cases, however, limitations of such a right could be allowed by the existence of compelling reasons of general interest. One could refer to the compulsory licensing where a government allows someone else to produce the patented product or process without the consent of the patent owner.<sup>233</sup> Article 30 of the TRIPS Agreement states that:

*"Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties."*

The TRIPS Agreement does not give an exact description of the conditions that must be fulfilled in order to be able to issue a compulsory license. However, it does mention anti-competitive practices, national emergencies and other circumstances of extreme urgency, as possible grounds for compulsory licensing. Alike the possibility recognised for patents, the abuse of the freedom to extend an MA or the negative consequences of the

exercise of this freedom on health must be taken into account when taking appropriate measures. The implementation of such a measure must, however be justified by its necessity and proportionality. We do not envisage that this can go so far as to force authorisation of an indication by the MAH. Such a measure, in fact, is not required to provide access to the drug.

**A third party could in principle obtain a MA**, provided that he would fulfil all legal requirements linked to such application for authorization. In particular, this party should prepare the necessary MA dossier. As mentioned earlier, in practice, the third party may have no access to the active ingredient or on details on the production process because the producer refuses to provide it (mainly based on its intellectual property rights) and/or it may be too expensive for a third party to buy the product to conduct the necessary tests. Imposing the producer to grant effective access to the active ingredient to a third party to allow the latter to apply for a MA for an indication that the initial MAH would refuse to seek for it itself, seems disproportional. It may only be possible in cases where a compulsory license may be awarded or in cases of abuse of dominant position. Such a measure must necessarily be exceptional, especially to the extent where other off-label use government initiated 'health promotion' measures deemed not sufficient to reach the objective of public health (in terms of granting access to safe and effective drugs for patients in need) pursued by the authorities. Other, less invasive measures seem more appropriate to meet the objective of protecting and promoting the public health as pursued by the authorities.

In order to increase availability of medicinal products, in particular on smaller markets, article 126a of Directive 2001/83/EC provides that, in the absence of a marketing authorisation or of a pending application for authorisation for a medicinal product, **which has already been authorised in another Member State, a Member State** may for justified public health reasons authorise the placing on the market of that medicinal product. In such cases, the competent authority of the Member State has to inform the marketing authorisation holder in the Member State in which the medicinal product concerned is authorised, of the proposal to authorise the placing on the market under this Article. When a Member State avails itself of this

<sup>233</sup> WTO, *Compulsory licensing of pharmaceuticals and TRIPS*, [www.wto.org/English/tratop\\_e/trips\\_e/public\\_health\\_faq\\_e.htm](http://www.wto.org/English/tratop_e/trips_e/public_health_faq_e.htm).



possibility, it must adopt the necessary measures in order to ensure that the requirements for the labelling and package leaflet, classification of the medicinal product, advertising, pharmacovigilance and supervision and sanctions are complied with.

### 7.2.2 Information measures

For a sound off-label prescription, it is necessary that physicians are fully aware of the conditions of **“justified” off-label prescription. Information campaigns by public medicines authorities are excluded from the advertising-regulation.** Those are indeed elements of the promotion and protection of the public health missions entrusted to public authorities. To this extent, States are nevertheless responsible for their choices. Thus, they will engage their responsibility if they ignore the rights of the MAH. Once this promotion is justified by the role that falls to public health authorities, it must be the driving force of the approach. Since the off-label prescribing is before all the practitioner's choice, it is of an utmost importance that the prescriber is appropriately informed of the conditions of such an off-label prescription. **Many healthcare professionals are aware of the possibility to prescribe off-label. Some healthcare professionals, however, indicate not to be fully aware of the conditions framing the off-label prescription.**<sup>234</sup> If a deficiency exists in this regard, **it may be appropriate to support information campaigns targeted to physicians and pharmacists.** The possible ignorance of doctors – and consequently information to be provided – may relate both to regulatory constraints (what are the legalities of prescribing off-label) and to the scientific conditions. The information will therefore usefully address the following two elements:

<sup>234</sup> Nederlands Rijksinstituut voor volksgezondheid en milieu. Off-label gebruik van geneesmiddelen. Transparantie gewenst. [http://www.rivm.nl/Documenten\\_en\\_publicaties/Wetenschappelijk/Rapporten/2008/januari/Off\\_label\\_gebruik\\_van\\_geneesmiddelen\\_Transparantie\\_gewenst](http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2008/januari/Off_label_gebruik_van_geneesmiddelen_Transparantie_gewenst)

### 1. Regulatory information measures

It seems useful to remind physicians that the off-label prescription is authorized as a tool for the exercise of their therapeutic freedom and in some circumstances prescribing off-label is the only solution to practice in an appropriate way. The conditions for this exercise, i.e. the **need for sufficient scientific evidence assessed in the light of the specific therapeutic need of the individual patient and the need to document a patient's consent** need to be specified.

No formality is required for such information. It falls within the competence of the federal authorities, in respect of the organization of health care.

This information can be assured by any means, including the publicity given to this report. Newsletters by health or social security authorities may be considered. Doing so, it should be kept in mind that Governments are, like everyone else, responsible for their fault or misconduct. The content of these documents therefore need to be analysed with caution.

### 2. Scientific information measures

The second element is the knowledge of therapeutic fields where off-label prescribing can be identified. **Off-label prescription needs to be based on evidence supporting the off-label use for the respective individual case.** Health professionals should inform themselves through their scientific readings, and continuing their education on the evolution of science. This is, moreover, their own obligation. Yet, **physicians report the necessity to be appropriately informed on the issue of off-label prescription.**<sup>235</sup>

The collection of information by prescribers can be part of this scientific demonstration of sufficient evidence and support evidence based medicine. Such evidence collection may be organised in a more or less binding way (free transmittal of information up to mandatory notification). Existing information can be transmitted by individual physicians or harvested by (on top of the chain) an expert group established with the public authorities of health and social security or by independent researchers selected by means

<sup>235</sup> Nederlands Rijksinstituut voor volksgezondheid en milieu. Off-label gebruik van geneesmiddelen. Transparantie gewenst. [http://www.rivm.nl/Documenten\\_en\\_publicaties/Wetenschappelijk/Rapporten/2008/januari/Off\\_label\\_gebruik\\_van\\_geneesmiddelen\\_Transparantie\\_gewenst](http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2008/januari/Off_label_gebruik_van_geneesmiddelen_Transparantie_gewenst)



of a national tender (cfr. infra evidence generation). It is important, however, to seek a way of information gathering that is effective — providers must not "fear" this exchange of information. To this end, a form of anonymization of transmitted data could encourage this transmission. The collected data would be related to the medicinal product concerned and the modality of use. Insofar as possible, the reasons for prescribing off-label for a particular patient group would be added. The determination of the criteria for the harvesting of information should – in any case – be based on an assessment of their scientific merit.

The available information should be translated to user friendly, scientifically valid and population-specific guidelines or evidence summaries (cfr. UK<sup>236</sup>) published on a central website.

If, however, the authorities wish to conduct an information campaign, this is also possible. In this regard, social security and public health authorities have many tools that they can use to share information with the health professionals. In Belgium, the Belgian Center for Pharmacotherapeutic Information (BCFI) and the Federal Agency for pharmaceuticals and health products could play a role in collecting and centralising this information.

### The possible role of EMA

The European Parliament adopted on 22 October 2013 a resolution on the report from the Commission to the Council, on the basis of Member States' reports, on the implementation of the Council Recommendation (2009/C 151/01) on patient safety including the prevention and control of healthcare associated infections.<sup>237</sup>

The resolution calls on the European Medicines Agency (EMA) to draw up a list of off-label medicines which are used in spite of there being an approved alternative *"and to develop guidelines on the off-label use of medicines, on the basis of medical need and taking account of patient protection"*. The European Commission reacted to this: (...) *possible actions*

<sup>236</sup> <http://www.nice.org.uk/advice?type=esuom>

<sup>237</sup> <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+REPORT+A7-2013-0320+0+DOC+XML+V0//ENEP> reference : A7-0320/2013 / P7\_TA(2013)0435;

<sup>238</sup> <http://ec.europa.eu/health/files/committee/72meeting/pharm655.pdf>

*of EMA should be seen in an overall context and within the remit of its competences. Calling on EMA to draft a list of medicines used off-label in spite of approved alternative may not be representative, as not all Member States have the same approved medicinal products on their market (national marketing authorisation through decentralised procedures). In addition, in some Member States recommendations and guidelines have been developed regarding off-label use (...).*<sup>238</sup>

Notwithstanding the 'caveats' of the European Commission, it must be stressed that EMA has a role in ensuring that patients find safe and effective drugs on the market, through the centralised procedure for marketing authorisation. The management of off-label use could be seen as an extension of this central responsibility. EMA could as such play a role in the central referencing to national guidelines on off-label use or in the elaboration of a central population-specific database of off-label used drugs.

### Transparency in the dimensions of off-label use

Today, **information on the extent of off-label use is lacking as physician are mostly not obliged to indicate the off-label use on the prescription**<sup>239</sup> Furthermore, **in case reports of adverse events, the indications for use are often missing, so that it is unknown whether the safety issue was related to off-label use or not**. The non-transparency in the true dimensions of off-label prescription implies that **off-label related income for the pharmaceutical firm is a black box**. Firms benefit from the income generated by off-label use, without necessarily making additional (or very little) investments. As it is not obligatory to notify the off-label use (specific indication,...) on the prescription (except for chapter IV drugs NIHDI), the off-label use can technically be billed at the on-label price. Since a 2002 amendment in legislation, reimbursement of off-label use via the 'regular' system was facilitated (see 6.1.4). This would be illegal practice if the off-label prescription is not justified, since prescribers need to refrain from unnecessary costs for the social security system. Yet, in several situations,

<sup>239</sup> However, prescribers are supposed to indicate where medicinal products are prescribed outside their reimbursed indication. However, in practice, only little such complete prescription documents are drafted. Many practitioners will not indicate such restriction, in order to get their patient's treatment reimbursed or by neglecting or ignoring this obligation.



non-reimbursed off-label use is justified and in the interest of the patient. Although off-label reimbursement schemes for unmet medical need cases (unmet medical need program, SSF) and various options for –indirect-reimbursement for off-label use in routine practice exist an overall, solid framework on the assessment and reimbursement of “justified” off-label use is lacking.

Various options could be considered to render off-label use more transparent. The **government could implement an obligatory notification of off-label use through an infrastructure of electronic prescribing (“e-prescribing”) and electronic health (“e-health) records.** E-prescribing software could allow physicians to record and transmit the indication for a drug when they write their prescriptions. Confidentiality of data needs to be taken into account, as some patients might not appreciate it to have information on the indication transferred to the pharmacist. Other options to obtain insight in the magnitude of off-label use is to ask healthcare professionals in the field to identify categories of frequent off-label use in a specific domain.

Rendering off-label use transparent includes several opportunities. In the first place, physicians’ responsibility for the off-label use will become more visible which may lead to increased attention for ‘justified’ off-label prescription. However, **physicians may experience the visibility as a liability threat** or may be constrained to make the off-label use visible because the patient will sometimes no longer benefit from reimbursement. It is clear that the obligation to be more transparent should go hand in hand with measures ensuring that physicians feel confident about their ‘justified’ off-label prescription (e.g. guidelines on ‘justified’ off-label use) and that continuity of access to safe and effective off-label products is guaranteed. **Transparency of off-label use is also necessary to identify where the need for a particular use of a product is situated.** This may be a primordial step in the selection process for government sponsored or co-sponsored trials (cfr. Infra).

### 7.2.3 Reimbursement

States are free to ensure the health protection on the basis of their own choice. However, in accordance with the applicable law, such decisions must be reasoned. They must therefore be based on proper reasons and thus be relevant to the aim pursued.

Purely financial grounds cannot justify such decision. Making an authorised product available for off-label use by granting reimbursement for individual patient cases under the responsibility of a healthcare professional, however, can be justified. From a scientific point of view this decision must be defensible. This means in particular that the off-label prescription can be validly seen as an acquired standard. As stated above, **the off-label use requires a sufficient scientific basis and informed consent of the patient.** The MA-requirement is in fact the standard response to the balance between protection of human health and economic freedoms of undertakings. To this extent, the off-label prescription should always be assessed against this standard. It is only on the ground of an imbalance in this basic equation that this measure can be adopted. The required scientific evidence to justify a reimbursement decision of a national authority would be the evidence that would reasonably justify an extension/variation of the MA.

### 7.2.4 How can evidence be generated? Government/firm co-financed trials

The current reality is that the medical industry is sponsoring most of the clinical trials needed to market its products because the industry profits from the benefits of performing such trials e.g. by obtaining market approval and to support their reimbursement request. In such cases, one may expect they will also take the responsibility to perform these studies. However, in many off-label situations, research questions of interest for patients and society exist for which the industry has no interest to perform the necessary trials. The central question is, therefore, **how and when can off-label research assessing safety and efficacy be generated, if firms omit to undertake the necessary research.**





One could think about shifting the responsibility to generate these data to the government, by means of sponsored trials.<sup>240</sup> Collaboration in evidence generation on the European level could have an added value in this. Firms, however, benefit from the off-label sales, as they can currently be billed at the on-label tariff, while no or little additional investments are made. As such, completely dismissing firms from the responsibility to invest in research, would undermine the point of the regulation of drug marketing. In this regard, we think it is reasonable to shift part of the cost of the data collection to the firm that uses data and benefits from the income from the off-label sales. It should be remarked, however, that pharmaceutical firms are theoretically not capable to differentiate the price according to the indication, since the information on the extent of off-label prescription is lacking.

Given the limited budget of the government for public funding of clinical trials, choices have to be made. It seems necessary to agree beforehand which type of off-label use to consider. To this end, a college of experts can search the literature to identify new possible off-label indications. Efforts could be centralised at the European level. In this regard, one could consider a European Network for off-label use assessment. The college of experts performing the assessment could be initiated by any stakeholder (public health authority, social security, university, practitioners, patients, industry). Reasonably, this referral would need to include the reasons justifying the request. Different factors can play a role in the priority setting of government sponsored or co-sponsored trials:

#### Available evidence

When the current off-label use of a product exceeds a significant threshold, this may be a good indication that it makes sense to evaluate safety and efficacy. Because of the extended use, it will be probable that there is already some evidence available that the use is effective and safe. Transparency on the actual dimensions of off-label use (cfr. supra) seems a primordial step in this. If evidence on efficacy and safety is already available or if there are indications of evidence; it can be worthwhile investing in co-

sponsored clinical trials, from a patient benefit point of view as well as from a governmental budgetary point of view.

#### Health impact (therapeutic need)

Sometimes, the off-label use will be more subtle because it concerns only small populations (e.g. rare diseases,.. ) and accordingly indications of evidence will sometimes be weak. In that scope, the possible health impact could be another element in the selection process. *While drug firms have an incentive to direct their efforts where it is most profitable, government should focus on health benefits. "An important factor in any such selection process would be the overall public health impact of the candidate drug. This factor would be measured by the relative burden of the underlying disease, by the availability of existing clinical options to treat the disease, by the need to stimulate greater competition within a given therapeutic class, and by the need to treat certain neglected diseases, including both rare or orphan diseases, by means that might otherwise not be developed absent government assistance."*<sup>241</sup>

As discussed above, several mechanisms are already set up to frame the use and the reimbursement of pharmaceuticals for unmet medical needs. Off-label used products could be submitted to a medical needs program, if no satisfactory alternative is available. At the moment of writing the report, however, it is not clear to what extent this system comes forward to the specificities of the off-label issues.

#### Societal need

Some might prefer to focus on the possible health impact and available evidence. Nevertheless, the resources for public funding are limited and should be invested efficiently trying to optimise the return on investment. The question rises, however, whether it can be justified to set up government-sponsored trials for societal need, i.e. if it can substantially reduce disease-related public expenditures, without jeopardizing the outcomes for the patient. This is particularly the case when an effective authorized pharmaceutical is available but at a much higher cost than a

<sup>240</sup> Neyt M, Christiaens T, Demotes J, Hulstaert F. Publicly funded Practice-oriented Clinical Trials. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 246. D/2015/10.273/53.

<sup>241</sup> Lewis T, Reichman J, So A. Treating Clinical Trials as a Public Good: The Most Logical Reform;





potentially equally safe and effective cheaper (off-label) alternative. On the one hand, granting access to cheaper, equally effective and safe pharmaceuticals to patients in therapeutic need serves public health interest, in terms of access to care and the sustainability of an offer of sufficient healthcare. Moreover, as in practice in some domains, off-label use is (widely) practiced anyway, it may be preferable to use it in a managed environment of clinical trials. On the other hand, patients could be unnecessarily faced to safety issues if they are included in trials related to the off-label product, if a safe licensed alternative already exists. Although, safety in the on-label indication may be established, this does not (necessarily) cover a safe off-label use as factors as age of the patient, comorbidities, use of concomitant medication, drug interactions could be different in the off-label and on-label use. This argument, however, also applies for pharmaceutical firms engaging in clinical trials for a new indication where a licensed alternative already exists.

As stated above, the competent authorities should refrain from circumventing the EU-regulation and undermining the effectiveness of this regulation (Laboratoires CTRS case). As such pro-actively setting up government-sponsored trials solely to reduce disease-related public expenditures, seems to be impossible under the current regulatory framework.

#### Compatibility with existing early access mechanisms

Compassionate use and medical need programs are designed to grant to patient early access to promising investigational pharmaceuticals or indications outside of a clinical study setting. Patients who seek access to these pharmaceuticals do so either because standard treatments have failed or they cannot tolerate approved medications, and because they are unable to participate in a clinical study. In that scope, they might be complementary with off-label "candidates", such as for instance repurposed drugs. From a governmental point of view, it should thus be considered how encouraging compassionate use of promising pharmaceuticals by granting compensation for the cost of the pharmaceutical and supporting of the off-label use of an existing product by sponsoring trials can be complemented. For compassionate use as well as for medical need programs an MA application must have been submitted or phase III clinical trials are ongoing. This implies that at least some evidence regarding the safety and efficacy of the product must already be available for the product to be eligible for the

compassionate use or medical needs programme. As such, the minimum level of evidence justifying the selection for a government-sponsored trial should be reflected on.

If government-sponsored trials are considered, the MAH could be invited to support and to participate to the research program.

- If the MAH is willing to support and participate, this firm would enjoy incentives for applying for variations for their MA if the evidence turns out to be sound. The MAH would, subject to his participation to the process, gain access to the data as soon as he would start a clinical trial and provided that those data are compliant with a research protocol. As firms benefit from the income generated by off-label use, without necessarily making additional investments, it seems a reasonable option to co-fund the research by money generated from a clawback of the income generated by the off-label use.
- If the firm does not wish to support the research program, the program could however be started. Given, where appropriate, economies of scale for the relevant MAH or an increase of his turnover, a specific fee would be required, to partially cover the cost of the measure. In addition, the firm could not benefit from the raw data collected through this program, so that these data could not be used in a clinical study designed to obtain, subsequently, an extension of a marketing authorisation. It should be noticed that the conducting of a research program always includes some involvement of the firm since it needs to distribute the products. If it concerns a real, specific medical need, however, possibilities to "force" a marketing or even, to have a compulsory licensing could be considered.

For those studies, a protocol should be prepared and the study would be carried out under the clinical trial regulations.

#### **Level of evidence in government sponsored trials**

The question rises **which level of evidence on clinical effectiveness should be obtained in (government-sponsored) trials, especially for drugs targeting small groups of patients**. Due to the small number of patients, clinical studies are rarely sufficiently powered to detect significant results on hard clinical endpoints. Moreover, the natural history of the disease is usually unknown, as physicians only have limited experience with the disease. However, in 2006, the EMA Committee for Human Medicinal



Products CHMP developed guidelines on clinical trials in small populations.<sup>242</sup> The guidelines acknowledge that in circumstances where only few patients are affected by a disease, a trial enrolling several hundred patients may not be practical or possible. Meanwhile it is stated that “*most orphan drugs and paediatric indications submitted for regulatory approval are based on randomised controlled trials that follow generally accepted rules and guidance.*” The guidelines state that “*deviation from such standards is, therefore, uncommon and should only be considered when completely unavoidable and would need to be justified.*”

In the UK, NICE evaluates orphan drugs using the same methods and decision criteria as for all technology appraisals, but a lower level of evidence may be accepted for orphan drugs.<sup>243</sup>

The Clinical trials Regulation recognises **low-intervention trials** as trials that pose only a minimal additional risk to subject safety compared to normal clinical practice.<sup>244</sup> This is particularly **the case where the investigational medicinal product is covered by a marketing authorisation, that is the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure** or, if that product is not used in accordance with the terms of the marketing authorisation, that use is evidence-based and supported by published scientific evidence on the safety and efficacy of that product, and the intervention poses only very limited additional risk to the subject compared to normal clinical practice. Those low-intervention clinical trials are often of crucial importance for assessing standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. According to the Clinical trials Regulation, those clinical trials should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products. In order to ensure subject safety they should however be subject to the same application procedure as any other clinical trial. The **published scientific evidence supporting the safety and efficacy of an**

**investigational medicinal product not used in accordance with the terms of the marketing authorisation could include high quality data published in scientific journal articles, as well as national, regional or institutional treatment protocols, health technology assessment reports or other appropriate evidence.**

Clinical trial regulation is originally designed for large-scale therapies. It is completed by pharmaco-vigilance regulation, aiming to have a continuous evaluation of potentially dangerous products. Where scarce scientific resources are available, additional care should be taken. Public policies to be based on scientific evidence, therefore should always take into account a balanced approach: where little evidence is available, only specific, case-by-case situations should be addressed by policy-makers. Where larger evidence is generated, a more comprehensive and active policy can be envisaged.

#### Evidence-based information and reimbursement

**Once sound evidence is established by government sponsored trials, the public authorities could publish the scientific results in order to inform health care professionals on the off-label use and reimbursement could be granted to make the off-label used product available for individual patients under the physician's responsibility.** These measures come forward to the interests that need to be met: access to safe and effective drugs to patients in need. As such the option to grant to a third party the right to apply for an MA is not necessary and would be disproportionate according to the target, although an extension of the market authorisation remains the best option in terms of legal certainty for all parties involved.

<sup>242</sup> Committee for Medicinal Products for Human Use. Guideline on clinical trials in small populations. In: EMEA, editor; 27 July 2006. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003615.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf)

<sup>243</sup> McCabe C, Claxton K, Tsuchiya A. Orphan drugs and the NHS: Should we value rarity? *British Medical Journal* 2006;99(5):341-5.

<sup>244</sup> Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC



## 8 CONCLUSION: TOWARDS A MANAGED OFF-LABEL USE IN BELGIUM

In contrast with authorised use of pharmaceuticals, scientific evidence on safety and efficacy for off-label use is sometimes lacking. Yet, off-label use is widely practiced, especially when there is no alternative available. The existing initiatives on the European level to frame off-label use and measures to stimulate research for new modalities do not always seem to be successful. On the national level several measures primarily targeting an optimal protection of patients' health, can be considered for a managed off-label use of pharmaceuticals,

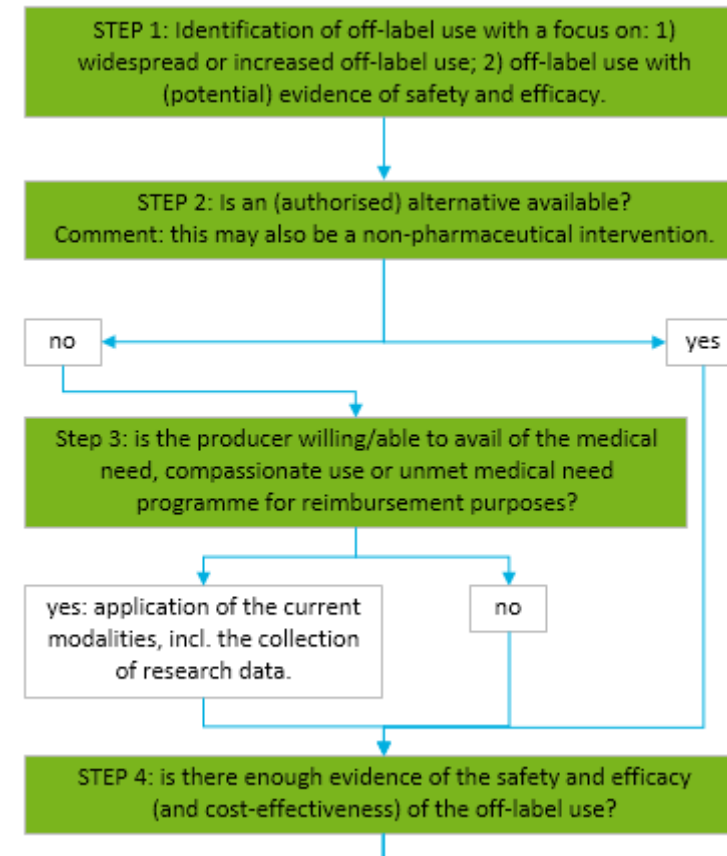
### 8.1 Stepwise assessment scheme

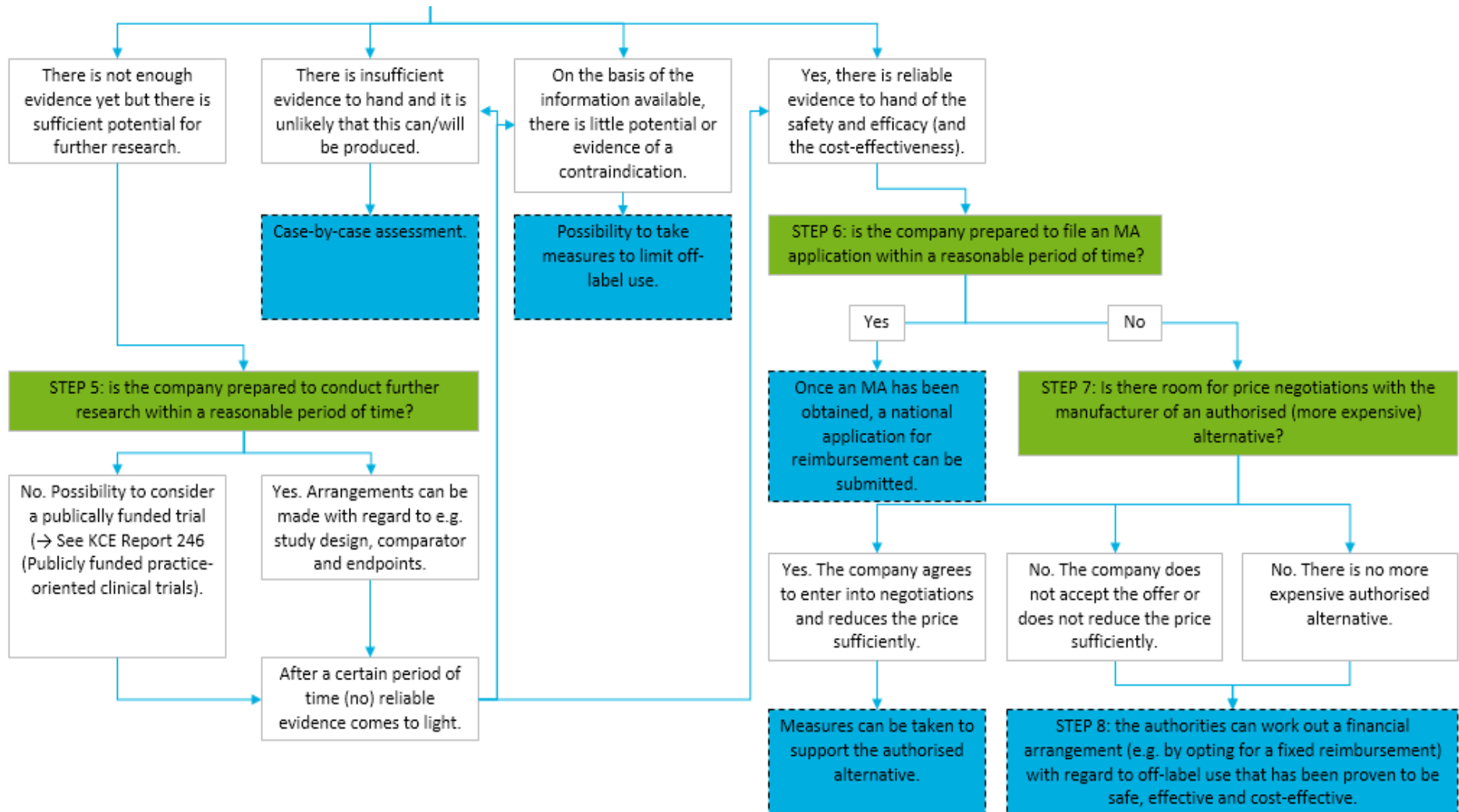
Based on the foregoing, the KCE proposes a step-by-step plan that could help policy-makers in the healthcare sector to assess and/or generate scientific evidence to ensure the safe, effective and targeted off-label use of medicinal products (Figure 1).

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

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

Figure 1 – a step-by-step plan to support a better managed off-label use of drugs.







### 8.1.1 Step 1: identification of off-label use

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

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

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

- Reporting off-label use with potential evidence of safety and efficacy:

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

### 8.1.2 Step 2: is an (authorised) alternative available?

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

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

The off-label use of a medicinal product for a condition for which there is no authorised medicinal product available can be authorised in the pre-commercialisation stage via a compassionate use or medical need programme, and may be reimbursed via the unmet medical need programme.

Manufacturers must be willing to file an application for this or at least be prepared to lend their cooperation. Besides, manufacturers can put a stop to a medical need or compassionate use programme at any time.

In cases where an application for a compassionate use or medical need programme is submitted, it is essential that the authorities set out the data collection terms to ensure that they also obtain the data they are particularly interested in. Currently, applicants are asked to supply data in the same format as required for an MA file. The risk-benefit assessment is also performed in the same mindset as MA applications or current clinical trials are evaluated.

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

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

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

As the safety and efficacy of off-label use take centre stage, it is also essential that these elements are evaluated. In the short term, that could be done on the basis of the evidence that is available already. In the longer term, research data collected within the framework of one of the above modalities (see step 3) could be used. The medical aspects can be evaluated at European (EMA) and at national level (FAMHP, NIHDI, KCE, others...).





At FAMHP<sup>245</sup> there already exists today a procedure where applicants, at charge of a fee, may request scientific or technical advice concerning the research and development of medicinal products for human use in the prospect of a possible application for clinical trials, MAs, variations of already commercialized medicines or line extensions.<sup>246</sup> For this advice, experts in the domain may be invited. This advisory procedure could be extended to evaluate off-label used products. For the aspect of quality, this evaluation should be done centrally by the FAMHP since the necessary data for this evaluation are not always publicly available.

Specifically for **innovative (off-label) therapies in oncology**, an advisory committee of experts becomes more and more necessary because of the rapid and complex evolutions in the domain. In oncology, many of the new drugs are targeted specifically at molecular characteristics specific for the tumor. Some of these targeted drugs are already reimbursed by the health insurance.<sup>247</sup> One challenge is the off-label use of these drugs in cancer of another type but which, however, exhibit the same molecular abnormality.

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

- a) There is not enough evidence to hand as yet to formulate a reliable conclusion on the safety and/or the efficacy (and, as the case may, the cost-effectiveness) of the therapy but there is enough potential to indicate that the impact of the therapy will be favourable. → Proceed to step 5.
- b) There is insufficient reliable evidence to hand and it is unlikely that this can/will become available in the short term. → Case-by-case evaluation to check whether the use should be supported and which measures could be taken. Elements that could be taken into

consideration are the severity of the condition, the alternatives available, the size of the population, the cost of the intervention (both to the authorities and to the patient), budget impact, etc.

- c) If, based on current knowledge, the off-label use has a low probability of being beneficial to the patient, it would be wiser not to support the use in question. And if there is evidence of contraindications, it would be best to restrict off-label use altogether. This could be effected by advising against the off-label use in a practice guideline issued by a professional organisation of doctors. Another option would be that the competent bodies (FAMHP or EMA) list the off-label use as a contraindication on the leaflet. On occasions, the FAMHP already publishes warnings with regard to off-label use within the framework of pharmacovigilance. → In these cases the step-by-step plan ends unless new evidence and information comes to light to change this stance, with the result that a new evaluation becomes desirable.
- d) Yes, there is enough reliable evidence to hand to support the off-label use. → Proceed to step 6.

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

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

- If the manufacturer is prepared to engage in further research, arrangements could be made about study design, the relevant comparator(s) and endpoints, for instance.

<sup>245</sup> [http://www.fagg-afmps.be/nl/MENSELIJK\\_gebruik/geneesmiddelen/geneesmiddelen/wetenschappelijk\\_technisch-advies/](http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/wetenschappelijk_technisch-advies/)  
Such a procedure also exists at EMA: [http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/regulation/general/general\\_content\\_000049.jsp%26mid%3DWC0b01ac05800229b9](http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/regulation/general/general_content_000049.jsp%26mid%3DWC0b01ac05800229b9)

<sup>246</sup> This is an MA in the name of the same holder where, for example, the pharmaceutical form and/or strength differs from one or more other medicinal products for which this licensee already has an MA.

<sup>247</sup> Van den Bulcke M, San Miguel L, Salgado R, De Quecker E, De Schutter H, Waeytens A, Van Den Berghe P, Tejpar S, Van Houdt J, Van Laere S, Maes B, Hulstaert F. Next generation sequencing gene panels for targeted therapy in oncology and haemato-oncology. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 240. D/2015/10.273/26.



- If the manufacturer declines, he cannot be forced to conduct a clinical trial on the safety and efficacy of the off-label use of his product.

In cases where a study like this would be of sufficient interest to society and the manufacturer has no (financial) interest in conducting a clinical trial himself, the authorities could consider providing the necessary funding (see KCE report 246 Publicly funded Practice-oriented Clinical Trials<sup>248</sup>) once the FAMHP has confirmed that the non-clinical file warrants a clinical trial in the new application. This non-clinical part is a.o. relevant if the new indication is an application for chronic use and applications for one-off use only have been authorised because, in that case, the toxicology would be different. The effect of the medicinal product should then for instance be examined in extended animal tests.

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

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

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

#### *8.1.6 Step 6: Is the manufacturer prepared to apply for a MA?*

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

In some cases, the manufacturer may not have the relevant rights to develop an off-label indication. As patent holder, the manufacturer is, in principle, the only one entitled to exploit the medicinal product. But he may sell a user

right - a license - to third parties. So, in principle, several manufacturers could have a license for a different therapeutic indication of one and the same product.

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

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

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

- The manufacturer is prepared to file an MA application. Once the MA is finally granted, off-label use is no longer an issue and the traditional procedure for (the extension of) a reimbursement can be started up.
- The manufacturer does not want to file an MA application. → Proceed to step 7.

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

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

<sup>248</sup> Neyt M, Christiaens T, Demotes J, Hulstaert F. Publicly funded Practice-oriented Clinical Trials. Health Services Research (HSR) Brussels: Belgian



In the case of negative evidence, the off-label use could then be listed as a contraindication in the leaflet.

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

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

- The manufacturer is prepared to reduce the price of the authorised medicinal product sufficiently. If there is little difference in the added value of the interventions, this would lead to a price reduction in the neighbourhood of the price level of the cheapest alternative. In this case, the authorities could reward the manufacturer of the authorised alternative by no longer supporting the off-label use of the unlicensed medicinal product financially.
- The manufacturer is unwilling to enter into negotiations about the price of the authorised product or the negotiations do not produce the desired result. → Proceed to step 8.
- If one or more authorised alternatives are available which are not more expensive than the off-label product, this step is irrelevant and step 8 can be proceeded to.

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

<sup>249</sup> Art. 56, §2, 1° of the Law regarding the compulsory health and disability insurance coordinated on the 14<sup>th</sup> of July 1994, *B.S./M.B.* 27 August 1994: The insurance committee can negotiate agreements limited in time and/or

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

- Art. 56 Agreement<sup>249</sup>

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

- In hospitals: lump sum per patient suffering from a certain condition

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

The decision to opt for a particular medicinal product will always remain the doctor's to take. What matters is that he informs the patient about the off-label use and that the latter gives his informed consent. In this way, responsibility is shared between doctor and patient.

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

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

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

field of application and aiming at the financial contribution for special models including an experimental way of prescribing, care provision or financing of medical care.



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

## 8.2 Conformity of the proposed scheme with EU legislation

The EU pharmaceutical regime is based on the principle that medicines must be of sufficient quality, safety and efficacy, but also sets very specific standards for demonstrating compliance with the principle (including the details in Annex I to Directive 2001/83 and the numerous EMA guidelines) and specific procedures for assessing that compliance (including powers of the EMA and the Commission to decide on specific issues at the EU level).

Member States are vested with the powers to set their own healthcare policy priorities provided these do not contravene or circumvent EU legislation. They have complete autonomy when it comes to deciding where public resources are spent.

The support of off-label use, especially where authorised alternatives are available, falls between interests of public health in terms of accessibility, where economical aspects – in times of budgetary restraints - play a role and a European regulatory system that is set up to support research and development of new, safe medicines, which also serves public health interests. The proposed scheme seeks to carefully draw the balance between these different and at the same time complementary interests and could help member states to ensure safe and effective off-label use.

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

- Publicly funded trials facilitate access to safe medicinal products and proactively prevent harmful and widespread off-label use. As such, the managed (non-) use of off-label products should lead to an optimal protection of public health as more information on the off-label use will be available for the parties involved. On the contrary, unmanaged and non-transparent off-label use may compromise patients' health. Although according to the pharmacovigilance rules, adverse events related to off-label use need to be reported, this is only an a posteriori action. The overall use and its implications remains unevaluated.
- Reimbursement of off-label use is considered only if there is sufficient clinical and non-clinical scientific evidence to hand during the assessment (comparable to the evaluation of MA applications). Where there is insufficient evidence or if the evidence is stacked against the off-label use, its use is banned or limited to certain, justified cases which, in turn, also ensures optimum protection of public health. MA holders are actually consulted every step of the way. Financial support from the authorities for evidence-based off-label use is considered only if all other options have been exhausted. In this sense, the proportionality of the measure is also guaranteed.

The final and exclusive decision-making powers to use a medicinal product in an individual case remain with the doctor, after he has obtained the patient's informed consent. The proposed measures do not prevent the patient from making the best possible personal therapeutic choice. In the individual therapeutic choice, cost consideration can also play a role for the patient. In particular cases where orphan drugs are not reimbursed, patients will have to bear the costs themselves or choose for a cheaper off-label alternative.<sup>250</sup>

<sup>250</sup> Caffeine Sterop 25mg/2ml and Peyona (the latter is registered as an orphan drug) are indicated for the 'treatment of apnoea in premature newborns'. Yet, both are used off-label to prevent apnoea in premature babies. Peyona is

more expensive and must be covered by the parents because it is an orphan drug and, as a result, does not qualify for the flat-rate hospital scheme. For that reason, the off-label use of the cheaper Caffeine Sterop 25mg/2ml is opted for.

