Pharmaceuticals

This section updates readers on the latest developments in pharmaceutical law, giving information on legislation and case law on various matters (such as clinical and pre-clinical trials, drug approval and marketing authorisation, the role of regulatory agencies) and providing analysis on how and to what extent they might affect health and security of the individual as well as in industry.

Promoting the Off-label Use of Medicines: Where to Draw the Line?

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I. Introduction

In Europe, medicines can only be marketed once they have passed through a strict regulatory process, designed primarily to protect patient safety. It is only after in-depth testing on the targeted disease population, including three phases of clinical assessment and clinical trials, that a medicine will obtain a 'marketing authorisation'. Given its primary goal of ensuring patient safety, EU law only allows a few narrow exceptions to the requirement of a marketing authorisation. A drug can only be used "off-label", meaning outside the limits of its marketing authorization, in authorised clinical trials or under one of the strictly defined exceptions, such as severe public health risk, compassionate use for groups of patients or for individual patients on a named patient basis.

However, in recent years, a trend has emerged among Member States to push the boundaries of the existing regulatory system, and actively promote the off-label use of medicines on the ground that they are cheaper than the alternative, authorised medicine. It is questionable whether this trend is in line with EU law.[1] The present article analyses and offers a critique of the latest development in this direction, which is the report of the Belgian "Health Care Knowledge Centre" (KCE), a federal scientific organisation tasked with advising policy-makers on decisions relating to health care and health insurance, on the management of off-label drugs (the **Report**).[2] The Report presents options for a framework for "better managed" off-label use of medicines in Belgium, and also at the European level. However, this article argues that, despite noticing the constraints imposed by EU law on the possibility of Member States to promote off-label use, the Report is premised on an inaccurate analysis of EU case law. The Report supports the wide-spread use of off-label use for reasons of cost-effectiveness, which plainly contradicts the case law of the EU courts. The approach put forward by the Report undermines both the EU regulatory system for approving medicines (i.e., the requirement for a marketing authorisation) and the national pricing and reimbursement systems (including HTAs[3]) that exist around Europe. As such, we argue that the approach suggested by the Report is not just erroneous as a matter of law; it may also be questionable as a matter of policy.

II. Overview of the Report

The Report "*intends to formulate options for a framework for a better managed off-label use of medicines for Belgium*" (p. 11). The Report starts by giving an overview of the existing legal framework related to the issue of off-label use at the European level, in Belgium and in a selection of other European and non-

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1 See for example, James Killick and Pascal Berghe, *Should cost prevail over safety? The risks of promoting unauthorised pharmaceuticals and off-label use for budgetary considerations,* [2014] 13 (5) Bio-Science Law Review 172, March 2014.

2 KCE Report 252, "Towards a better managed off-label use of drugs", 29 September 2015, available on the Internet at https://kce.fgov.be/publication/report/towards-a-better-managed-off-label-use-of-drugs#.VgrNYGZXeJI (last accessed on 21 October 2015).

3 Health Technology Assessment ("HTA") is an important part of evidence-based health decision-making in most EU countries. It provides policy-makers with objective information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective.

European countries. It concludes that while EU law forbids public health measures that stimulate or authorise off-label use of medicines for purely financial reasons (though its statement sin this regard are qualified by some of its other comments – see below), it does not require Member States to prohibit the prescription or administration of medicines off-label and Member States "*are free to foresee specific reimbursement mechanisms to make off-label products available in individual patient cases under the responsibility of the prescribers*" (p. 45). The Report then assesses to what extent certain government supported measures to manage off-label use would be feasible, i.e. (i) granting the right to apply for a marketing authorisation to a third party, (ii) supporting information campaigns targeted to physicians and pharmacists, (iii) reimbursing medicines used off-label or (iv) financing off-label research assessing safety and efficiency (p. 83-89). Finally, the Report 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*" (p. 90-96) which will be discussed in detail in section IV below.

III. The Report Contains an Erroneous and Contradictory Analysis of EU Law

The report recognizes that "*based on the underlying concern for patient safety, EU law foresees limited possibilities for the use of non-authorized medicinal products*" (p. 22). Indeed, the EU regulatory framework provides for only a few, narrow exceptions to the requirement of compulsory prior marketing authorisation. A drug can only be used outside the limits of its marketing authorisation (i) in authorised clinical trials or (ii) under one of the strictly defined exceptions in either Directive 2001/83[4] or Regulation 726/2004,[5] such as particular severe public health risk, compassionate use for groups of patients, or for individual patients with what the Report calls "special needs", i.e., based on their own individual diagnosis.[6]

However, the Report is wrong to suggest (p. 32) that the need for a marketing authorisation is a question of "*balance*"[7] because regulatory restrictions such as the need for a marketing authorisation are only validated to the extent that they are necessary and proportionate to the protection of human health and safety. This appears like a downgrading of the most fundamental regulatory requirement in Europe, namely that a marketing authorisation should be granted before medicines are marketed or used. The harmonised EU regulatory system aims at guaranteeing the highest level of patient safety through the use of compulsory marketing authorisations. The exceptions to the requirement to obtain a specific marketing authorisation before using any medicine to treat any given disease must thus be interpreted narrowly.[8] The exceptions are not to be interpreted based on balancing of public health and freedom of undertakings to market their products. The case law could not be clearer: public health is paramount and takes precedence over any economic considerations.[9]

The Report also errs in trying to draw (p. 23) a distinction between off-label use of authorised medicines (i.e., not in accordance with their marketing authorisation) and the use of unauthorised medicines. There is no legal difference: in both cases, the medicine is not authorised for the use in question, but can be prescribed by a doctor based on his or her clinical judgment of that individual patient.[10] The fact that a medicine is not authorised for any indication (meaning the EMA or national regulatory authorities have not reached a positive conclusion on its safety for any indication) would be a relevant consideration for the doctor; it does not change the legal standards to be applied.

This can be seen in the *CTRS* judgment, which held that "*off-label prescribing is the sole responsibility of the prescribing physicians*".[11] This principle was also

4 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, OJ L 311, 28.11.2001.

5 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ [2004] L 136/3.

6 See Report, p. 22 and the articles cited therein.

7 Between protection of public health and freedom of undertakings to market such product.

8 See Case C-185/10, *Commission v Poland*, EU:C:2012:181.

9 See, e.g. Case C–180/96R, *UK v Commission (BSE)*, §§ 91-93 ("*paramount importance to be accorded to the protection of health*") and Case T–13/99, *Pfizer v Council*, at § 456 ("*The protection of public health, which the contested regulation is intended to guarantee, must take precedence over economic considerations*").

10 Based on Article 5(1) of Directive 2001/83/EC.

11 Case T-452/14 *CTRS v Commission*, EU:T:2015:373, § 82.

stated in the *Novartis Pharma*[12] and *Commission v Poland* judgments: the decision to prescribe off-label medicines is the decision of prescribers, and can only be done in "*individual situations justified by medical considerations*",[13] following "*an actual examination of his patients and on the basis of purely therapeutic considerations.*"[14] In other words financial or budgetary reasons should play no part in the doctor's clinical decision to prescribe off-label.

In the *CTRS* case, the EU General Court ("GC") held that prescribers, when exercising their therapeutic freedom, should not be induced by public authorities to prescribe drugs for indications that are off-label. This judgment was taken in the context of an orphan drug benefitting from a 10-year exclusivity period in application of Regulation 141/2000.[15] The GC annulled the decision to grant a marketing authorisation for a generic drug based on the fact that the evaluation report and the SmPC for this drug contained multiple references to the fact that the generic would be effective for treating the orphan condition. The GC stated that, even though off-label prescribing by a doctor is not prohibited, or even regulated, by EU law, a market authorisation should not be formulated in a way to "*induce a prescribing physician to prescribe a medicinal product for therapeutic indications [off-label] and for which a market authorisation has already been granted for another medicinal product that benefits from the market exclusivity*" in order to ensure the effectiveness of the orphan drug exclusivity.[16] The *CTRS* case criticised inducement or encouragement by authorities that undermined the effectiveness of one rule under EU law, namely that orphan drugs benefit from a period of exclusivity. The same analysis would equally apply to authorities inducing or encouraging doctors to prescribe off-label for financial rather than therapeutic reasons, contrary to the principles clearly set out in the CJEU's judgment in *Commission v Poland*. The Report does acknowledge that off-label use, as an exemption from the marketing authorisation requirement, should be: "*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.*"[17] However, the Report nevertheless proposes measures to induce doctors to prescribe off-label, for economic reasons. For example (p. 95), the Report notes that a lump sum could be provided to hospitals that is slightly higher than the cheapest off-label alternative. While the Report then goes on to claim that "the decision to opt for a particular medicinal product will always remain the doctor's to take", it is clear that the doctors will have a strong financial incentive to prescribe off-label under the proposed scheme as they would only be funded "slightly" more than the cost of the off-label product.[18]

As noted above, this type of inducement/encouragement is very similar to what the CJEU struck down in the *CTRS* case, in which the CJEU clearly opposed the situation where "*[the responsibility of prescribers] could in practice be attenuated by the presence [...] of statements that the product is effective and safe for treating other therapeutic indications than those for which its marketing authorisation has been granted.*"[19] The attenuation of the prescriber's individual clinical responsibility that the Report proposes is much more direct than in the *CTRS* case: the *CTRS* case was concerned about statements in the evaluation report and SmPC about the efficacy of another product to treat the orphan indication, while the Report concerns a financial mechanism that would in effect force the doctor to prescribe off-label, failing which the hospital will lose out financially (and the doctor would potentially face criticism from his or her managers). So the principles laid out in the *CTRS* case would apply and lead to the conclusion that this suggestion by the Report is contrary to EU law.

The Report does refer to the *Commission v Poland* case,[20] and indeed cites the key part of that judgment: "*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.*"[21] However, the Report then proceeds to downplay these statements by suggesting that *"restrictions based solely on economic reasons are not accepted, but could*

12 Case C-535/11, *Novartis Pharma GmbH v Apozyt GmbH*, EU:C:2013:226, § 48.

13 Case C-185/10, *Commission v Poland*, § 34.

14 Case C-185/10, *Commission v Poland*, § 35. (emphasis added)

15 Regulation 141/2000 of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1.

16 Case T-452/14 *CTRS v Commission*, § 80. (emphasis added)

17 Report, p. 22. (emphasis added)

18 See Report, p. 95.

19 Case T-452/14 *CTRS v Commission,* § 82

20 Case C-185/10, *Commission v Poland*.

21 Report, p. 41.

they be if they are linked to the financial balance of the social security system or the integrity of the national health system?" [22] This is again erroneous as a matter of EU law.

Indeed, this very point was explicitly addressed by the CJEU in the *Commission v Poland* case. The CJEU rejected Poland's argument based on the "balance of the social security system". The Report seems to turn a Nelsonian blind eye[23] to this passage of the judgment:

> *"46. It is also necessary to reject the argument of the Republic of Poland that the importation and the placing on the national market of a medicinal product cheaper than the equivalent medicinal product which has obtained marketing authorisation may be justified by financial considerations, inasmuch as they are necessary both in order to ensure the financial stability of the national social security system and to allow patients who have only limited financial means to have access to the treatment which they need.*
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> 47. It must be noted in that respect, first, that although EU law does not detract from the power of the Member States to organise their social security systems and to adopt, in particular, provisions intended to govern the consumption of pharmaceutical products in order to promote the financial stability of their health-care insurance schemes, the Member States must, however, comply with EU law in exercising that power (Joined Cases C-352/07 to C-356/07, C-365/07 to C-367/07 and C-400/07 A. Menarini Industrie Farmaceutiche Riunite and Others [2009] ECR I-2495, paragraphs 19 and 20).
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> 48. It must be pointed out, next, **that Article 5(1) of Directive 2001/83 is not concerned with the organisation of the health-care system or its financial stability**, but is a specific derogating provision, which must be interpreted strictly, applicable in exceptional cases where it is appropriate to meet special medical needs.
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> 49. Finally, the Member States remain competent to set the price of medicinal products and the level of reimbursement by the national health insurance scheme, on the basis of health, economic and social conditions, as is apparent from Article 4(3) of that directive.
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> *50. Article 5(1) of the directive cannot therefore be relied on to justify a derogation from the requirement for a marketing authorisation for reasons of a financial nature."*[24] (emphasis added)

The Report (p. 42) also refers to the *ABPI* case[25]and cites a paragraph of the judgment which may lead the reader to believe that the EU Court considered legal a financial incentive scheme encouraging off-label use. However, this citation is taken somewhat out of context. The APBI characteristics of the scheme at issue in that case did not encourage off-label use; What it encouraged was "*the prescription of certain medicinal products belonging to the same therapeutic class as those previously prescribed or those which might have been prescribed to patients if the incentive scheme did not exist, but which do not contain the same active substance*" (emphasis added).[26] In other words, a doctor was encouraged to choose authorised medicine A over authorised medicine B, where the two medicines were in the same therapeutic class, i.e. were authorized for the same indication. This scheme concerned primarily the prescription of "statins", a class of medicines authorized and prescribed for reducing cholesterol and the aim was to persuade doctors to prescribe a cheaper off-patent statin rather than a higher priced statin that was still patent protected. This case is not therefore support for an incentive scheme directed at encouraging off-label use.

The Report also tries to support its argument by discussing a number internal market cases[27] which provide for derogations to the rules on the free movement of goods on certain public policy grounds. Based on this, the Report reaches the general conclusion that "*It seems to follow from* [the *Asturias*] *judgment that restrictive measures are possible to ensure an equal access to medicines of good quality for everyone."*[28] But this judgment concerned a national provision limiting the number of pharmacies per area with a view to ensuring that the public had reliable and good quality provision of medical products by pharmacists, notably even distribution of pharmacies

22 Report, p. 42.

23 See https://en.wikipedia.org/wiki/Battle_of_Copenhagen_(1801) (last accessed on 21 October 2015).

24 Case C-185/10, *Commission v Poland*, §§ 46-50.

25 Case C-62/09, *Association of the British Pharmaceutical Industry ("ABPI") v Medicines and Helathcare Products Regulatory Agency,* EU:C:2010:219.

26 *ABPI* case, § 17.

27 Report, p. 42, referring to the *Doc Morris* and *Asturias* cases.

28 Report, p. 42.

throughout the national territory, thus ensuring that the population as a whole has adequate access to pharmaceutical services.[29] These cases are far removed from what is proposed in the Report, i.e. not applying key parts of the regulatory system for budgetary reasons. It is well-established in free movement of goods cases that public health must take precedence over financial or economic considerations.[30]

In any event, the case law on the free movement of goods also requires that restrictive measures be necessary and proportionate to achieve public policy goals. Given that the EU Member States already have pricing and reimbursement systems and HTA processes, which aim at ensuring affordable and equal access to medicines,[31] it is not obvious that off-label use would be necessary or proportionate and thus not justified under that free movement case law. In addition, it is not obvious that (and the Report does not explain why) off-label prescribing of a (presumably) limited number of medicines would have a major budgetary impact and ensure equal access to medicines to everyone.

Moreover, the Report does not explain why the free movement rules would be relevant to the general promotion by a Member State of off-label use. Normally, the rules on the free movement of goods would not apply to measures affecting all actors within the national territory in the same manner.[32]

More fundamentally, Member States cannot invoke public policy derogations to prevent the free movement of goods in areas which are already harmonised by specific EU legislation.[33] Here, Article 5(1) of Directive 2001/83 already lays down specific situations when Member States may derogate from the general requirement that medicinal products can only be sold under a valid marketing authorisation. The CJEU has clarified when that derogation can be applied in the specific context of prescribing medicines for non-authorised indications for economic reasons. Member States cannot rely on the public policy exceptions found in the free movement rules to widen the specific derogations permitted under Directive 2001/83.[34] Even if ensuring access to medicines and ensuring the financial balance of the social security system may be grounds for a public policy derogation under the free movement rules, these are not relevant considerations under Article 5(1) of Directive 2001/83.

The internal market cases and the ABPI case cited by the Report thus rather confirm the errors of EU law contained in the Report. The tensions in the Report can be seen by the contradictory conclusions at the end of its discussion of EU law. On the one hand it acknowledges that "*[EU law] 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*", but on the other hand affirms that "*This does not imply, however, that any role for public authorities in the management of off-label use is excluded*" and still refers to *"financial accessibility."*[35] The former statement is correct; the latter is not.

IV. The Report Proposes Wide-spread Off-label Use for Reasons of cost-effectiveness and thus Undermines the Regulatory System for Approving Medicines

The Report concludes with a proposal for *"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"*.[36] The Report recommends that decision makers take the following 8 steps:

– Step 1: Identification of off-label use with a focus on (i) widespread or increased off-label use, (ii) off-label use with (potential) evidence of safety and efficacy;

29 Cases C-570/07 and C-571/07, *Asturias*, ECLI:EU:C:2010:300, notably at § 78.

30 See, e.g., Case C-180/96R, *UK v Commission (BSE)*, §§ 91-93, where the CJEU stressed the "paramount importance to be accorded to the protection of health".

31 These systems already balance the needs of individual patients with the financial resources available to treat the entire population (see Report, p. 44), so there is no need for authorities to have recourse to off-label use for the same purpose.

32 The CJEU in Joined Cases C-267/91 and C-268/91 *Keck and Mithouard* (EU:C:1993:905) held that national price controls which apply to all relevant traders operating within the national territory and affecting in the same manner, in law and in fact, the marketing of domestic products and those from other Member States, constitute "selling arrangements" falling outside the scope of the free movement rules. *Keck* clearly applies to the scenario contemplated by the Report, i.e. general encouragement of off-label prescribing for budgetary reasons applying to all actors and affecting them in the same manner.

33 Case 174/82, *Sandoz,* EU:C:1983:213.

34 See to this effect Case C-143/06, *Ludwigs - Apotheke München Internationale Apotheke v Juers Pharma Import-Export GmbH*, EU:C:2007:656, §§ 32 – 33.

35 Report, p. 44.

36 Report, pp. 90-96.

- Step 2: Is an (authorised) alternative available?
- Step 3: Is the producer willing/able to avail of the medical need, compassionate use, or unmet medical need programme for reimbursement purposes?
- Step 4: Is there enough evidence of the safety and efficacy (and-cost effectiveness) of the off-label use?
- Step 5: Is the company prepared to conduct further research within a reasonable period of time?
- Step 6: Is the company prepared to file an MA application within a reasonable period of time?
- Step 7: Is there room for price negotiations with the manufacturer of an authorised (more expensive) alternative?
- Step 8: Options as regards financial support for off-label use.

Of the eight steps of the plan, three relate to cost-effectiveness. Step 4 considers the question, "*Is there enough economic evidence of the safety and efficacy (and cost-effectiveness) of the off-label use*?" Step 7 considers the question "*Is there room for price negotiations with the manufacturer of an authorised alternative?*" and Step 8 offers as a final objective that "*the authorities can work out a financial arrangement (e.g. by opting got a fixed reimbursement) with regard to off-label use that has been proven to be safe, effective and cost-effective*". So the Report encourages the wide-spread use of off-label drugs, for cost reasons, notably to put pressure on the manufacturers of authorised drugs during price negotiations.

Indeed, the Report goes further and proposes that: *"If off-label use is scientifically substantiated and cost-effective, the authorities could provide financial support to facilitate the use of the product".*[37] The Report advocates that cost-effectiveness is a legitimate reason for the use of off-label drugs: "[...] *the cost of the authorised medicinal product being much higher than the off-label alternative may be important drivers."*[38]

Such an approach – i.e. permitting and promoting the sale of unauthorised medicines on cost grounds – is on its face incompatible with EU law, as discussed above. It would also have the effect of undermining the regulatory system. By encouraging off-label uses that have not been subject to the same rigorous controls and safeguards as on-label medicines, Member States such as Belgium bypass the regulatory process and undermine the European Union's underlying objective of guaranteeing patient safety.[39] Moreover, unilateral deviations from EU law by Member States may lead to a fragmentation of the EU regulatory framework for medicines, which could prevent the rapid diffusion of new medicines across Europe and undermine the ability of companies to innovate and grow across Europe. The Report's overall undermining of the fundamental requirement of the regulatory system can be seen in the passage where it says the need for a marketing authorisation is a question of "balance" between public health and an undertaking's freedom to market its products. As noted above, this should not be a question of balance: the case law says public health comes first.

V. The Report Omits to Mention the Existing Pricing and Reimbursement (and HTA) Systems around Europe

One striking feature of the Report is that it says nothing about the Belgian or European pricing and reimbursement bodies, which take decisions under the relevant laws that seek to balance the short term interest in lower prices against the long-term incentive for innovative drug development, while taking account of factors such as the cost of developing the medicine. Nor does it mention Health Technology Assessments, prevalent around Europe, which judge if a medicine is good value for money given the clinical benefits it brings, based on the likely outcome to the patient and cost and effectiveness of previously existing treatments.[40]

Across Europe, on-label treatments have gone through this process and been approved by the relevant authorities for pricing and reimbursement after their expert technical assessment. It is not the case that the prices for such treatments are set unilateral-

37 Report, p. 94.(emphasis added)

38 Report, p. 9-10.

39 See, for instance, recital 7 of Directive 2001/83: "*The concepts of harmfulness ond therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorisation for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.*"

40 For more information on the role of HTA in the EU, please refer to http://ec.europa.eu/health/technology_assessment/policy/index_en.htm.

ly by the companies. EU Member States typically have the power in this process to seek a lower price if they deem it excessive or not justified or indeed to deny reimbursement altogether based on the criteria of national law, and while respecting the rules in the EU Transparency Directive.

The Report does not consider these existing and rather developed processes. It instead proposes that medicines whose prices have been accepted by those processes should reduce their prices further because of off-label medicines or be largely replaced by off-label medicines. This approach would undermine the legitimacy of the pricing and reimbursement processes around Europe. Once the price and reimbursement level of a medicine has been approved via those processes, it should not be for other public bodies to intervene and second-guess those processes and the resulting decisions. Instead, the price and reimbursement level of the authorised medicine should be reviewed under the existing pricing and reimbursement system or HTA rules.

Such an approach would also harm innovation. While the Report often cites Lucentis and Avastin as an example of the perceived issue (with some remarks about the drugs' common origin[41]), it does not address the impact that off-label prescription could have on other innovative players in this clinical field, notably on Regeneron, whose Eylea product is the latest treatment in this area. The Report seems to suggest that Regeneron's innovation should be rejected and not funded. What signal does that send, and what effect does that have on innovation?

There is one point that is covered briefly in the Report that merits closer scrutiny, namely the relevance of the size of the dose in this debate. Pricing and reimbursement schemes look at the price of the dose needed to have the requisite clinical impact on the patient. They do not look at the price per millilitre of product. The appropriate way to assess pricing and reimbursement levels is per level needed to achieve a clinical impact.

The off-label debate set forth in the Report is by contrast more focused on pricing per millilitre, as can be seen in the comparison of the price of Lucentis with that of off-label Avastin on a per millilitre basis.[42] As the Report acknowledges, a much bigger volume of product is needed for intravenous treatment of some forms of cancer (Avastin's approved indication) than for the intraocular treatment of wet AMD (Lucentis' approved indication and Avastin's off-label use). What the Report does not say is that if one looks at the cost per treatment (in the authorised indication), Avastin is more expensive than Lucentis – both prices having been approved by the relevant pricing and reimbursement bodies. So the difference in price between Lucentis and off-label Avastin is largely due to the fact that drugs are normally priced on the basis of the cost per treatment rather than the cost per millilitre.

That leads to a second concern, rightly identified in the Report, that the push for off-label use of such medicines could have unintended consequences. For example, a push toward off-label use for a medicine whose authorised indication requires a higher volume dosage than the off-label use could simply result in the withdrawal of the authorised indication (as was the case for Campath).[43] Alternatively, if the authorised indication is the lower volume dosage, the company may be reluctant to seek approval for a new indication where the volume dosage is much higher, because the cost of that higher dosage indication would have to be very high to be aligned (in volume terms) with the prices for the existing indication.[44] Given that the high dosage volumes may be in oncology, [45] this would be an unfortunate consequence for patients. It is ironic that the only reason that neither of these consequences have occurred for Avastin and Lucentis is the fact that the MA holders for the two drugs in Europe are different companies: the split ownership that the Report notes has been the subject of complaints[46] is in fact what enables

41 It is noteworthy that no competition authority anywhere has taken issue with the contractual arrangements between Genentech, Roche, and Novartis that resulted in Roche having the rights over Avastin and Novartis having the rights over Lucentis in Europe. Indeed, many of the passing references to competition law in the report are inaccurate, notably the idea that a compulsory licensing could be ordered as a matter of competition law (e.g., Report, p. 83), something that would be manifestly inconsistent with the CJEU's case law – see e.g. C-418/01, *IMS Health*, ECLI:EU:C:2004:257. For a fuller analysis of the competition issues, see *Killick and Berghe* "Pharmaceutical sector: can non-authorised products be considered included in the relevant market for the assessment of alleged anticompetitive conduct? A short analysis of the recent Italian Avastin-Lucentis decision," *Journal of European Competition Law & Practice* (2015) 6(2) pp. 102-109. The one point on which the Report is correct is that competition law would not impose any obligation on any undertaking to apply for an MA for an off-label use (Report, p. 94).

42 Report, p. 12.

43 Report, p. 17.

44 Report, p. 81.

45 Report, p. 81.

46 Report, p. 15.

the off-label use of Avastin to take place without the unintended consequences that will result in many other scenarios if this policy becomes widespread. The policy recommendations of the Report – most notably the decision tree / flowchart[47] – fail to take any account of these potential unintended consequences, despite them being noted in passing in the Report.

VI. The Report Fails to Address all the Relevant Policy Considerations

Although aiming to be a study that will inform Belgian policy-makers, there are several important policy considerations which are not dealt with in any detail in the Report. For instance, it does not consider the impact that wide-spread off-label use will have on research & development in the pharmaceutical sector, and the risk that it will lead to fragmentation of the EU regulatory framework for medicines (see above).

Even when it comes to the fundamental objective of ensuring public health, the Report is somewhat ambiguous. It recognises the risks inherent in off-label use, stating that "*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*".[48] It also refers to the Mediator story.[49] Such public health considerations should suggest caution before encouraging wide-spread off-label use, yet the Report recommends its promotion.

In view of the importance of economic considerations discussed above, it is questionable whether the Report lives up to its claim that its proposal "*clearly prioritises the protection of public health over and above economic, budgetary considerations*".[50] The Report's conclusions define public health in terms of accessibility (i.e. cost), rather than limiting the use of products in circumstances when the efficacy, safety and quality cannot be assured: "*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.*"[51]

VII. Conclusion

We have noted a number of errors in the way the Report analyses the applicable provisions of EU law. More generally, in view of the EU regulatory framework and its primary objective of protecting patient safety, it seems inappropriate under EU law for public authorities to encourage the wide-spread off-label use of medicines, since this would interfere with doctors' individual professional assessment as to what treatment is justified on therapeutic grounds. If the Belgian authorities were to adopt such a policy of encouraging/promoting off-label use on a general basis driven predominantly by economic considerations, its legality would be highly questionable as a matter of EU law. Moreover, and as explained above, the Report could undermine the European Marketing Authorisation system and the national systems of pricing and reimbursement. It may also have unintended and counter-productive consequences. Further reflection is clearly called for.

47 Report, pp. 90-91.

48 Report, p. 8.

49 Report, p. 8.

50 Report, p. 96.

51 Report, p. 96.