

GMC Decides Not to Relax Its Guidelines to Permit Broader Prescribing of Off-Label and Unlicensed Medicines, Including on Cost-Saving Grounds

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Introduction

Across Europe, as public budgets are tightened, there is pressure to lower spending on prescription medicines. These well-understandable budgetary pressures have led to some controversial suggestions, notably proposals to ease the rules on the prescription of off-label medicines to save costs where off-label drugs are cheaper than the drugs approved for the condition in question. On the whole, these proposals have not been adopted because of concerns about putting cost-cutting ahead of patient safety and because of legal concerns, such as those highlighted by the European Court in *Commission v. Poland* earlier this year. This article looks at one such example involving the prescription guidance of the UK General Medical Council (GMC) as well as exploring the issue more generally.

The 2011 GMC Consultation on Proposed Changes to Its Prescription Guidance

In 2011, the GMC proposed making changes to its "Good practice in prescribing medicines," the guidance it offers to doctors in prescribing medicines and which supplements the GMC's core guidance on "Good Medical Practice."

The proposal suggested that it might be appropriate to allow doctors to prescribe unlicensed or off-label medicines if they were "satisfied, on the basis of authoritative clinical guidance, that [the medicine] is as safe and as effective as an appropriately licensed alternative." This would apply even when

a licensed product was available. The proposal noted that some medicines are routinely prescribed off-label, usually because there is no appropriate licensed alternative" but also because there are cheaper medicines that are as safe and effective."

This was a break from the previous (2008) Guidance which limited the prescribing of off-label or unlicensed medicines to circumstances where there is no appropriately licensed alternative and, in relation to off-label prescribing, where the doctor is "**satisfied that [such a medicine] would better¹ serve the patient's needs than an appropriately licensed alternative.**" The 2008 Guidance suggested that this would most frequently arise in relation to prescribing for children given that (historically) pharmaceutical companies did not test their medicines on children and therefore did not have approval for use of their medicines to treat children.²

The 2008 Guidance thus started from the principle that, whilst off-label prescribing may be appropriate in limited circumstances, it is not to be considered routine when a licensed drug is available. The key principle in the 2008 Guidance was that off-label prescription was only justified when it could better serve the patient's needs than the licensed alternative. By contrast, the 2011 proposal suggested that routine off-label prescription could be justified on economic grounds ("cheaper medicines that are as safe and effective").

The GMC put out the proposal to public consultation in May 2011.



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1. Authors' emphasis.

2. See http://www.gmc-uk.org/guidance/ethical_guidance/prescriptions_faqs.asp#10.

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Reactions to the Consultation

The consultation revealed a divergence of views on the proposal. A number of respondents supported the proposal on the basis that this could save money by using (often older) off-label medicines to avoid prescribing a higher-cost, licensed product. Concerns about patient safety, however, were voiced by a number of respondents. For example, the Association of the British Pharmaceutical Industry³ expressed concerns about the inclusion of financial considerations in prescribing guidelines and noted that the proposal could lead to inappropriate prescribing of unlicensed drugs or off-label use. Other respondents noted that there were questions about whether the proposed guidance was compatible with European law (a question which we will explore briefly below). The UK Medicines and Healthcare Products Regulatory Agency (MHRA) was notably one of those opposed to the change to the guidance.

The GMC Decided to Drop the 2011 Proposal and Stick With Its 2008 Guidance

Following the consultation, the GMC decided to drop its proposed amendments and to retain the existing 2008 Guidance, unchanged, in relation to off-label prescribing.⁴

Given the concerns that the proposal might be in breach of EU law on the use of medicines, the GMC sought legal advice. This advice confirmed that under EU law unlicensed medicines could only be prescribed where there was a 'special need' and that this could not be taken to encompass unlicensed medicines for patients with rare conditions if there were a licensed alternative or circumstances in which commissioning bodies did not support the funding of a licensed alternative. The legal analysis in relation to off-label products (i.e., under what conditions could drugs be prescribed off-label other than if there were no licensed alternative) was described as complex legally. As a result, the GMC decided to retain its previous 2008 Guidance.⁵

The EU Legal Framework

We will briefly explore the applicable EU law framework to give background to the GMC's decision.

The general principle: medicines must be approved before they are put on the market

EU law requires that a medicinal product has to receive a specific marketing authorisation before it can be put on the market. Article 6 of Directive 2001/83/EC⁶ provides as follows: "No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or unless an authorisation has been granted in accordance with Regulation (EC) 726/2004." The marketing authorisation stipulates the indications for which the medicine is authorised.

Based on the underlying concern for patient safety, EU law foresees only limited possibilities for the use of non-authorised medicinal products:

- In authorised clinical trials, as set out in Directive 2001/20⁷
- Under one of the exceptions in Directive 2001/83 and Regulation 726/2004,⁸ namely:
 - compassionate use for groups of patients where there is no other treatment available (Article 83 of Regulation 726/2004)
 - compassionate use for an individual patient on a named patient basis, at the individual request of a patient or a physician, and under the physician's supervision (Article 5 of Directive 2001/83)
 - where a conditional marketing authorisation is granted to a product under Article 14(7) of Regulation 726/2004, as implemented by Commission Regulation 507/2006⁹
- Off-label use under the individual decision of a treating physician

3. <http://www.abpi.org.uk/our-work/policy-parliamentary/Pages/gmc.aspx>.

4. http://www.gmc-uk.org/6b_Guidance_on_Prescribing.pdf_48443029.pdf.

5. http://www.gmc-uk.org/6b_Guidance_on_Prescribing.pdf_48443029.pdf at points 19-23.

6. Directive 2001/83/EC on the Community code relating to medicinal products for human use, as amended, [2001] OJ L 311/67.

7. Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, [2001] OJ L 121/34.

8. Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended [2001] OJ L 136/1.

9. Commission Regulation 507/2006 on the conditional marketing authorisation for medicinal products or human use falling within the scope of Regulation (EC) No 726/2004 [2006] OJ {2006} L 92/6.

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While off-label use as such is not defined in either Directive 2001/83 or Regulation 726/2004, provisions of EU law make clear that the scope of the off-label use exception is limited. In particular, the exception contained in Article 5(1) of the Directive states that a 'Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility'. This provision makes it possible for a doctor to prescribe an unauthorised medicinal product or to prescribe an authorised product off-label, that is, to treat a condition for which the medicine is not authorised. This exception implements the generally recognised principle of therapeutic freedom for prescribing physicians.¹⁰ 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.

In sum, none of the exemptions to Article 6 of Directive 2001/83 (which requires that medicines be authorised) authorises a general promotion of off-label use. This is confirmed by the provisions of Article 5(2) of Directive 2001/83, which allow Member States to temporarily allow an unauthorised product in the event of public health threats, such as bioterrorism, pandemic influenza, etc.¹¹ So as a matter of EU law, off-label use constitutes a strictly limited exception to the principle of compulsory prior-market authorisation.

National authorities, and bodies to whom they delegate regulatory powers (like the GMC under the Medical Act 1983), are bound by these EU law provisions and not entitled to widen the scope of the off-label use exception to cover broad situations such as when (for example) "there are cheaper medicines that are as safe and effective," but which are not authorised for the indication in question.

This is because, pursuant to Article 4(3) of the Treaty on the Functioning of the European Union, these bodies 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. Hence they cannot broaden the scope of the off-label use exception beyond the boundaries accepted by EU law.

The European Court's recent judgment in *Commission v. Poland* confirms that EU law only permits narrow exceptions to the rule that medicines must be authorised before being put on the market

The approach now taken by GMC is also in accordance with the recent ruling of the European Court of Justice in earlier this year (Case C-185/10, *Commission v. Poland*¹³). In that judgment, the European Court found that Poland failed to fulfil its obligations under Article 6 of Directive 2001/83 by keeping in force Article 4 of the Polish Pharmaceuticals Law which permitted the importation of unauthorised medicinal products, having the same active substances, dosage and form as authorised medicinal products already marketed, if the imported products were priced lower than the authorised equivalent products.

The Court started its analysis by emphasising that the derogations from the general requirement to hold a marketing authorisation must be interpreted strictly. Thus, the derogation under Article 5(1) allowing the possibility of doctors to prescribe non-approved medicinal products must remain exceptional in order to preserve the crucial role of the marketing authorisation procedure to protect patients' health.¹³

The Court noted that the 'concept of special needs' referred to in Article 5(1) of the Directive, applies only to "individual situations justified by medical considerations and presupposes that the medicinal product is necessary to meet the needs of the patient."¹⁴

10. This principle is confirmed in the European Commission's merger decision in the Sanofi-Aventis/Zentiva case which defines off-label use as the possibility "for a medicine to be used for non-approved indications at the discretion of the prescribing physician." See Case M.5253, decision of 4 February 2009, paragraph 14, footnote 6.

11. Article 5(2) reads as follows "2. 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."

12. Available at: <http://curia.europa.eu/juris/liste.jsf?language=en&num=C-185/10>

13. Judgment, paragraphs 31-32.

14. Judgment, paragraphs 33-34.

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The Court also stated, “the requirement that medicinal products are supplied in response to 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.”¹⁵ Therefore, Article 5(1) of Directive 2001/83 cannot be relied on to justify a derogation from the requirement for a marketing authorisation for financial reasons.¹⁶ The Court also stated that where an equivalent authorised medicinal product is available on the market, there exist no special needs for an unauthorised product.¹⁷

The European Court thus concluded that financial considerations, including the competitive pricing of a foreign product in relation to its national counterpart, cannot justify the placing on the market in a Member State of an imported unauthorised medicinal product. The Court thus confirmed previous case law stating that “paramount importance [should] be accorded to the protection of health,” meaning that under EU law public health takes predominance over financial or economic considerations.¹⁸ This is in line with the language of Article 168 TFEU, which states that “a high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities.”

Conclusion

The GMC’s proposed changes to its prescription guidelines are but one example of the challenges faced by public authorities with responsibility for medical matters given the need to cut costs. The GMC’s decision to retain its previous 2008 Guidelines seems a wise one, not least given the difficulties under EU law with the approach suggested in the 2011 Proposal. Other public authorities around Europe would be wise to follow its lead and avoid promoting unauthorised or off-label use of medicines on budgetary grounds.

EU law clearly provides that budgetary considerations must not lead public authorities to jeopardise the integrity of Europe’s regulatory system which aims at guaranteeing the highest level of patient safety through compulsory marketing authorisations. The European Court has confirmed that the exceptions to the need for a specific marketing authorisation before using any medicine to treat any given disease should remain strictly limited. And it has reaffirmed once more the fundamental principle that public health must be put before financial considerations.

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15. Judgment, paragraph 35.

16. Judgment, paragraph 38.

17. Judgment, paragraph 37.

18. See, for example, Case C-180/96 R, *UK v. Commission* (BSE), [1996] ECR I-3903, paragraphs 91 to 93 and Case T-13/99, *Pfizer Animal Health v. Council*, at paragraph 456 “The protection of public health, which the contested regulation is intended to guarantee, must take precedence over economic considerations”