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Prescription of Unlicensed Medicines or Unlicensed Indications in England & Wales

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1 Background

Directive 2001/83/EEC provides, at Article 6, that "*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) No 726/2004*" (by the European Commission under the centralised procedure)[1].

Article 5 of the same Directive allows Member States to adopt provisions, excluding medicinal products supplied in response to an unsolicited order, to the specification of a medical practitioner for use in a particular patient, from the requirements of Article 6. The EU framework as a whole therefore, does not preclude the prescription of an unauthorised product or the prescription of an authorised product for an unauthorised indication (here described as "off-label" prescription) at the discretion of the doctor and at his own responsibility. Such prescription has always occurred in circumstances where no authorised product was available to treat the condition suffered by the particular patient. However, it may also take place where the product authorised for a specific indication is more expensive than a similar product which has not been so authorised, in order to reduce costs.

2 Implications for Liability of Producers Under the Consumer Protection Act 1987

The Consumer Protection Act 1987, which implemented the EU Product Liability Directive (85/374/EEC) into UK law, provides that the producer is liable in respect of damage caused by a defective product. A product is regarded as being defective if "*the safety of the product is not such as persons generally are entitled to expect…*"[2]. In determining what persons generally are entitled to expect in relation to a product, all the circumstances shall be taken into account, including the presentation of the product, any instructions or warnings in relation to the product and "*what might reasonably be expected to be done with or in relation to the product*"[3].

The concept of reasonable use will readily be related to the approved recommendations and, therefore, it would be argued by a producer that the existence of a defect could not be inferred from the fact that damage resulted from off-label prescription, unless the producer had promoted the product off-label (which would be contrary to the advertising provisions of Directive 2001/83/EEC as further discussed below) making an unauthorised indication a de facto recommended use of his product. Even then, liability would only arise if the information provided by the producer was not a proper reflection of current knowledge concerning the product. The provision of information in response to a specific request by a healthcare professional is not to be equated with promotion, assuming the response is factual, accurate and balanced.

3 Potential liability of the prescribing doctor

A claim arising from off-label use of a medicinal product, may be brought in negligence or, in the context of treatment provided privately, in contract. Health Authorities, Trusts or companies running private hospitals will be vicariously liable for the acts or omissions of those they employ to provide care to patients.

3.1 Claims in contract

As indicated above, where private treatment involves the supply of a particular drug, a claim in contract may be based on an allegation that the use of a product off-label renders it not "reasonably fit for its purpose" under Section 4 of the Supply of Goods and Services Act 1982. In circumstances where a doctor or institution providing private care has a primary obligation in contract for injury flowing from the supply of a product in breach of the implied term of "fitness for a particular purpose", such a claim may be easier than one pursued against the producer of the product under the Consumer Protection Act 1987.

In addition, the Courts will imply a contractual term that the doctor will use reasonable skill and care in his treatment of a patient; the extent of the duty of care can, in practice, be treated as identical to that imposed by the tort of negligence.

3.2 Claims in tort

It is clear that the doctor owes his patient a duty of care to act with appropriate skill and caution in advising upon and administering a treatment. The tort of negligence is based on the omission to do something that a reasonable man, guided by the considerations that ordinarily regulate appropriate conduct, would do, or doing something that a reasonable man would not do.

In considering whether prescription of a medicine off-label was negligent or whether the patient was provided with appropriate counselling regarding such off-label use, the legal standard is that set out in Bolam v Friern Hospital Management Committee [1957] 2 All ER 118:

> "*A doctor is not guilty of negligence if he has acted in accordance with the practice accepted as proper by a responsible body of medical men skilled in the particular art.*

> *… Putting it the other way round, a doctor is not negligent, if he is acting in accordance with such a practice, merely because there is a body of opinion which takes a contrary view."*

Minor modifications of the test have been made in case law to reflect the fact that the Court defines the standard and, therefore, inappropriate conduct cannot be justified by the mere fact that a body of health professionals acts similarly. The practice must "rightly" be supported by an appropriate body of medical opinion. (see Bolitho v City and Hackney HA [1997] 3 WLR 1151.)

In general, if a patient is harmed by a product and the prescribing doctor acted in the best interests of the patient and in accordance with a reasonable body of medical opinion, the doctor and his employer are unlikely to be found liable - whether the product was used within the terms of the marketing authorisation or not. Moreover, even if it can be shown that no relevant body of responsible medical practitioners would rightly support a particular form of off-label use, the claim will fail if it cannot be shown that the injury actually resulted from the off-label use e.g. if the adverse event would have arisen even if the authorised product had been used.

There are few English cases directly concerned with the potential exposure of doctors in relation to unlicensed use of medicines.

- In Kennedy v Queen's Medical Centre, University Hospital NHS Trust (Unreported, 12 January 2001) a junior hospital doctor was found to have failed in her duty to explain to the patient, at the beginning of treatment with an unlicensed allergen, that there were certain risks attaching to treatment. In this context it was noted that it was incumbent upon clinicians dispensing an unlicensed treatment to exercise caution and to be alert to any reports of complications, more so than when using licensed drugs which had undergone extensive clinical trials for their indication. It was also said that it was the duty of the physician to provide the patient with information which enabled the patient to make a balanced judgement about treatment.
- Consistent with the test in Bolam, the High Court found that a physician was not negligent where a patient suffered injury after treatment with gentamicin despite the fact that the physician had used a dose in excess of that approved in the data sheet. The physician was able to produce evidence to indicate that the dose he used was consistent with a body of medical opinion which took the view that the approved data sheet erred on the side of caution (Vernon v Bloomsbury Health Authority see [1995] 6 Med LR 297).

3.3 Authoritative Guidance

Off-label use is widely accepted to give rise to extra responsibilities and risks.

The Medicines and Healthcare products Regulatory Agency ("MHRA") does not issue any specific advice to doctors in relation to off-label use, and states that its role is "*to ensure the safe use of medicines, not to comment on the way in which individual doctors use medicines*". However, past guidance issued in June 1985 (MAL 30) stated:

> *"…it shall be remembered that a practitioner prescribing an unlicensed product does so entirely on his own responsibility, carrying the total burden for the patient's welfare and, in the event of an adverse reaction, may be called upon to justify his actions. Under these circumstances it may be advisable for the practitioner to check his position with his medical defence union before prescribing such unlicensed products."*

Consistent with this is the content of a lead article in December 1992 in the Drug and Therapeutics Bulletin ("DTB", Volume 30, No 25) entitled "Prescribing unlicensed drugs or using drugs for unlicensed indications", which noted that the Medicines Act 1968 and European legislation preserve a doctor's "clinical freedom" to act as he sees to be in the best interests of the patient, including through the use of licensed medicines for indications or in doses or by routes of administration outside the recommendations given in the marketing authorisation, and that such products can be dispensed by pharmacists.

In relation to off-label use, the article described cases where such use may be independently justified. The examples given were cases where licensed indications did not reflect current knowledge or include well proven uses. Interestingly it also referred to a case where a licensed indication was said to be "*over restrictive and cost considerations might justifiably be taken into account*":

> *"Junifen and Brufen syrup both contain 100mg ibuprofen in 5ml liquid yet for Brufen the indications include use as an anti-inflammatory, and for Junifen as an antipyretic. Brufen costs much less than Junifen, and on cost grounds doctors would be justified in prescribing Brufen syrup for both indications."*

In relation to the practical implications, the DTB makes statements consistent with the above analysis of the law above:

> *"In using an unlicensed drug, or a drug in a way incompatible with the data sheet, the doctor must act responsibly and with reasonable care and skill. When prescribing outside a licence it is important the doctor does so knowingly, recognises the responsibility that such prescribing entails and when obtaining consent to treatment should, where possible, tell the patient of the drug's licensed status, and for an unlicensed product that its effects will be less well understood than those of a licensed product."*

The General Medical Council ("GMC") provides advice for doctors in relation to off-label prescribing in its guidance document, Good Practice in Prescribing Medicines (May 2006):

> *"19 You may prescribe medicines for purposes for which they are not licensed. Although there are a number of circumstances in which this may arise, it is likely to occur most frequently in prescribing for children…*
>
> *20 When prescribing a medicine for use outside the terms of its licence you must:*
>
> *(a) Be satisfied that it would better serve the patient's needs than an appropriately licensed alternative.*
>
> *(b) Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy. The manufacturer's information may be of limited help in which case the necessary information must be sought from other sources.*
>
> *(c) Take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring and any follow up treatment, or arrange for another doctor to do so …*
>
> *(d) Make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing the medicine."*

This GMC guidance goes on to deal with the issue of providing information to the patient about the recommended medication in the section "Information for patients about the licence for their medicines":

> *"21 You must give patients, or those authorising treatment on their behalf, sufficient information about the proposed*

course of treatment including any known serious or common side effects or adverse reactions. This is to enable them to make an informed decision…"

It follows from the above that, where there is an appropriately licensed alternative, the GMC does not support as good practice the use of a product outside the terms of its authorisation, unless a cogent case can be put forward that it better serves the needs of the particular patient. While the GMC's guidance document, "Good Medical Practice" advises doctors that, in providing care, they are required to "*make good use of the resources available*", this should not be interpreted as endorsing off-label prescribing and, regardless of the evidence base or experience for using a medicine off-label, it can be argued that cost alone is not a justification for turning away from use of the licensed product.

Finally, the Royal Pharmaceutical Society[4] confirms that supply of medicines by pharmacists consistent with the provisions of Article 3 of Directive 2001/83/EEC (which creates exemptions from the requirements under Article 6, for a medicine, placed on the market, to have a marketing authorisation) is permitted.

4 Promotion of Medicines for Unauthorised Indications

A further issue that may arise is where a health authority or Trust recommends off-label use of a medicinal product.

Article 87.2 of the Directive provides: *"All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics"*.

These requirements are reflected in the Medicines (Advertising) Regulations 1994, which implement these provisions of the Directive into UK law. Accordingly, Regulation 3A(1) provides:

"No person shall issue an advertisement relating to a relevant medicinal product unless that advertisement complies with the particulars listed in the summary of product characteristics".

Further confirmation is provided in the Code of Practice issued by the Association of the British Pharmaceutical Industry (the "Code") which states that *"the promotion of a medicine must be in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in the summary of product characteristics*" (clause 3.2). The supplementary information for this clause specifically states that "*the promotion of indications not covered by the marketing authorisation for a medicine is prohibited by this clause*".

Advertising is defined broadly in the legislation as encompassing all forms of promotion. The requirement for an advertisement to comply with the content of the SmPC applies to any "person" and accordingly, these provisions would seem to cover promotion of medicines by NHS bodies and private hospitals as well as by pharmaceutical companies. In these circumstances, the inclusion of recommendations promoting use of unlicensed medicines or licensed medicines for an unauthorised indication, in hospital guidelines or formularies, would appear to be unlawful. Support for this view is provided by MHRA's Blue Guide which states that while the principal responsibility for advertising material rests with the marketing authorisation holder, other persons may also be subject to sanction.

Finally, the definition of advertising would not include responses to unsolicited responses to requests for information, received by pharmaceutical companies in relation to their products, as long as such responses are accurate, balanced and up-to-date. The fact that such activities are not viewed as promotional is confirmed by guidance issued by the European Commission, advising companies that information should be provided to prescribers and patients in relation to use of unlicensed medicines supplied on a compassionate use basis[5] and that the potential for off-label use should be considered by companies when developing risk management plans[6].

5 Conclusion

In summary, a doctor may exercise his prerogative to prescribe an unlicensed medicine or a licensed medicine for an unauthorised indication, at his own responsibility. However, should the patient suffer injury as a result of an adverse event resulting from the use of a product in these circumstances, he is likely to have difficulty pursuing a claim against the producer of the product under the EU Product Liability Directive or the national legislation implementing its provisions, unless the producer has provided misleading or incomplete information regarding such unauthorised use of the product. However, the doctor or his employer, may be found liable for such prescription, if it is not supported by a responsible body of medical opinion.

While therefore NHS bodies may wish to encourage off-label prescription of any medicinal product, where a licensed alternative is more costly, they will also be concerned regarding potential exposure to claims, should a patient receiving such treatment, suffer injury. Furthermore, overt recommendations by NHS Trusts, health authorities and others, to use products off-label, may be contrary to the Medicines (Advertising) Regulations 1994.

Endnotes:

1 Limited exemptions from this requirement are provided at Article 3 (e.g. for use in clinical trials) and Article 5 (e.g. for compassionate use).

2 Section 3(1) Consumer Protection Act 1987.

3 Section 3(2) Consumer Protection Act 1987.

4 The Royal Pharmaceutical Society of Great Britain. The use of unlicensed medicines in pharmacy. Last reviewed September 2007.

5 Vol 9A of the Rules Governing Medicinal Products in the European Union: Pharmacovigilance for Medicinal Products for Human Use, Part I, Section 5.7.

6 Vol 9A of the Rules Governing Medicinal Products in the European Union: Pharmacovigilance for Medicinal Products for Human Use, Part I, Section 3.6.2.g.

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