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# THE USE OF DRUGS BEYOND (OFF-LABEL) AND WITHOUT (UNLICENSED) MARKETING AUTHORIZATION

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The use of drugs for off-label purposes is widespread. Surveys suggest that up to 1/4 of all prescriptions in palliative care come into this category.<sup>1,2</sup> In PCF, the symbol † is used to indicate such use. However, it is impractical to highlight all cases of off-label use, particularly when it is simply a matter of the route or dose being different from those in the manufacturer's Summary of Product Characteristics (SPC).

It is important for prescribers to understand that *marketing authorization* for drugs regulates the *marketing activities* of pharmaceutical companies, and not the prescriber's clinical practice. Even so, off-label use does have implications for prescribers, and these are discussed in this section.

The situation has become more complicated now that mixing two or more *licensed* drugs in a syringe for administration by continuous infusion is officially considered to produce an *unlicensed* preparation. However, such use in palliative care is often appropriate and will generally represent standard practice.

## Definitions

### Marketing authorization

Marketing authorization (MA) means that a drug has been approved by a regulatory body for use in humans and licensed for specific indications, and can be marketed by the relevant pharmaceutical company.

### Off-label use

Off-label describes the use of a drug beyond the specifications of its MA, e.g. for an unlicensed indication, or in doses, preparations, patient population or route not covered by the MA.

### Unlicensed drug

There is no simple definition of an unlicensed drug. Essentially it is a drug which does not have MA for medicinal use in humans. Unlicensed drugs include:

- a mixture of two or more drugs in a syringe for administration by continuous infusion (see p.665)
- 'specials' obtained from a commercial company with a 'specials' manufacturing licence, e.g. alfentanil solution for nasal/buccal administration (see p.769)
- preparations made in a local pharmacy at the request of a prescriber for an individual named patient
- drugs from a licensed manufacturer in the UK without MA in the UK, e.g. new drugs awaiting MA, or drugs for which MA has been abandoned, suspended or revoked, e.g. cisapride, oxetacaine, thioridazine
- drugs with MA in another country but not the UK and are imported
- new drugs undergoing clinical trials.

### The authorization (licensing) process

Before a drug can be marketed in the UK, it requires MA (previously product licence). There are four application procedures in the European Union:

- *centralized*, application evaluated by the European Medicines Agency (EMA); the European Commission grants a single MA valid for the whole European Union

- *decentralized*, simultaneous application made by several member states, with one taking the lead; if successful, national MA then being granted in each state
- *mutual recognition*, application for authorization in a member state when MA exists in another member state; the new member state relies on the original member state's evaluation as a basis for its decision
- *national*, application for MA in only one member state; in the UK the application is evaluated by the Medicines and Healthcare products Regulatory Agency (MHRA) on behalf of the Licensing Authority, a body consisting of UK health ministers.<sup>3</sup>

Certain drugs, e.g. for HIV/AIDS, cancer, neurodegenerative diseases, must be licensed through the centralized procedure. The UK Parallel Import Licensing Scheme also allows a drug authorized in other European Union states to be imported and marketed in the UK, if it has labels and a Patient Information Leaflet (PIL) in English.

In the UK, the MHRA evaluation comprises an evaluation of the efficacy, safety and quality of the drug from a medical, pharmaceutical and scientific viewpoint to ensure that it satisfies predefined criteria. Advice is sought from the Commission on Human Medicines (CHM), an independent advisory body, which in turn is assisted by specialist expert advisory groups.

At a European level, the Committee for Medicinal Products for Human Use (CHMP) fulfils a similar role to the CHM. New drugs will have relatively limited safety information and the pharmaceutical company is generally required to outline a risk management plan.

Restrictions are imposed if evidence of safety and efficacy is unavailable in particular patient groups, e.g. children. MA is granted for up to 5 years and then renewed following re-evaluation of the risks and benefits.<sup>3</sup>

Thus, the process ensures that in relation to the drug's authorized uses, there has been due consideration of its efficacy, safety and quality, that the benefits outweigh the potential risks, and that there is appropriate accompanying product information and labelling.<sup>4</sup> The MA defines the conditions and patient groups for which a pharmaceutical company can market and supply the drug, with more information about the drug's authorized uses provided by the manufacturer in the Summary of Product Characteristics (SPC).

However, the MA does not limit what the drug could be used for (i.e. off-label use), and clinical experience may reveal other indications. For these to receive a MA, additional evidence would need to be gathered and submitted. The considerable expense of this, perhaps coupled with a small market for a new indication, often means that a revised application is not made.

### Prescribing for off-label indications or unlicensed drugs

In the UK, the following may legally prescribe licensed drugs for off-label indications and unlicensed drugs:<sup>5-7</sup>

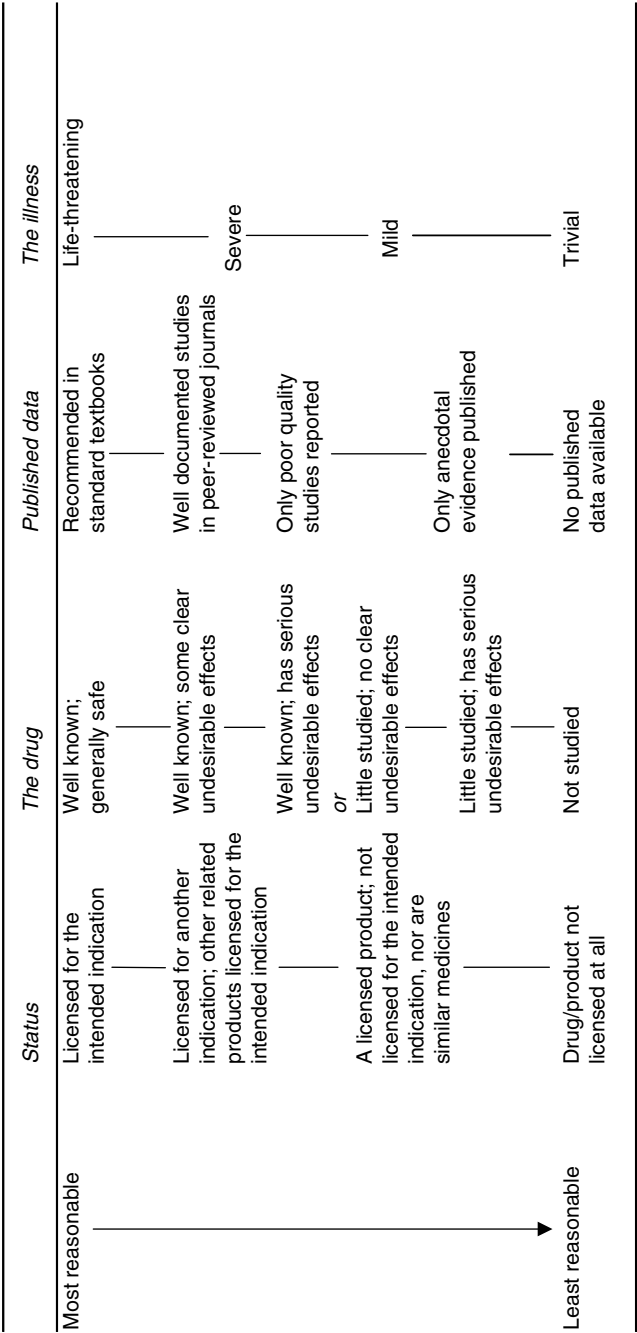
- doctors, specifically safeguarded in the UK Medicines Act 1968
- nurses, pharmacists, podiatrists, physiotherapists and radiographers who are registered as *supplementary prescribers*, provided it is done in the framework of an agreed Clinical Management Plan for a specific patient in partnership with a doctor or dentist
- nurses or pharmacists who are registered as *independent prescribers* if this is accepted clinical practice.

These prescriptions can be dispensed by pharmacists<sup>8</sup> and administered by nurses or midwives.<sup>9</sup>

In addition to clinical trials, such prescriptions may be justified:

- when prescribing generic formulations for which indications are not described
- with established drugs for proven but unlicensed indications
- with drugs for conditions for which there are no other treatments (even in the absence of strong evidence)
- when using drugs in individuals not covered by the MA, e.g. children
- when mixing drugs before administration, e.g. two or more drugs in a syringe for administration by continuous infusion.<sup>10,11</sup>

Any *independent prescriber*, including non-medical prescribers, can mix drugs and direct others to mix, as can *supplementary prescribers* when the preparation is part of the Clinical Management Plan for an individual patient. Current legislation on mixing does not extend to controlled drugs, although amendments are under consideration. Meanwhile, existing good practice arrangements should be followed in relation to mixing controlled drugs.<sup>10</sup> Preparations resulting from mixing drugs, other than when one product is a vehicle for the administration of the other, cannot be supplied or administered under Patient Group Direction arrangements.



**Figure 1** Factors influencing the reasonableness of prescribing decisions.

The responsibility for the consequences of prescribing a drug under such circumstances lies with the prescriber, who must be competent, operate within the professional codes and ethics of their statutory bodies and the prescribing practices of their employers.<sup>4-6</sup> The prescriber must be fully informed about the actions and uses of the drug, be assured of the quality of the particular product, and in the light of published evidence, balance both the potential good and the potential harm which might ensue.

It is possible to draw a hierarchy of degrees of reasonableness relating to off-label and unlicensed drug use (Figure 1). The more dangerous the medicine and the more flimsy the evidence the more difficult it is to justify its prescription.

The PIL will not contain information about unlicensed indications. Thus, it is important that prescribers (or those authorizing treatment on their behalf) provide sufficient information to patients about the drug's expected benefits and potential risks (undesirable effects, drug interactions, etc.) to enable them to make an informed decision (Box B). The GMC also recommends that when prescribing a drug off-label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorized alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the drug to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the drug prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the drug and for overseeing the patient's care, including monitoring the effects of the drug.

For off-label prescribing, monitoring can be delegated to another doctor, but not if the drug is completely unlicensed.<sup>12</sup>

Non-medical prescribers should ensure that they are familiar with their own profession's prescribing standards, e.g. NMC. Although the advice is broadly similar to that of the GMC, there are some differences.<sup>13,14</sup>

**Box B** Providing information for patients about the use of drugs beyond and without marketing authorization<sup>12</sup>

Some drugs are routinely used beyond their licence, e.g. when treating children. When current practice supports the use of a drug in this way, it may not be necessary to draw attention to the licence when recommending it.

However, it is good practice to give as much information as patients or those authorizing treatment on their behalf, require or which they may see as significant.

When patients, or their carers express concern, you should also explain in broad terms the reasons why the drug is not licensed for its proposed use. Such explanations may be supported by written information.

However, you must explain the reasons for prescribing a drug that is unlicensed or being used off-label when there is little research or other evidence of current practice to support its use, or when the use of the drug is innovative.

In palliative care, off-label drug use is so widespread that concerns have been expressed that a detailed explanation on every occasion is impractical, would be burdensome for the patient and increase anxiety, and could result in the refusal of beneficial treatment.<sup>15</sup> A recent UK survey of over 220 palliative medicine doctors showed that, when using a drug for a routine off-label indication, only 5% *always* mention this to their patients, and 31% *never* do. However, in situations where there is little evidence and limited clinical experience to support a drug's off-label use, these figures change to 57% and 7% respectively.<sup>16</sup>

This is a grey area and each clinician must decide how explicit to be; an appropriate level of counselling and a sensitive approach is essential. Some NHS Trusts and other institutions have policies in place and have produced information cards or leaflets for patients and caregivers (Box C). A position statement has also been produced by the Association for Palliative Medicine and the Pain Society (Box D).<sup>17</sup>

**Box C** Example of a patient information leaflet about the off-label use of a drug**Use of medicines beyond their licence (off-label)**

This leaflet contains important information about your medicines, so please read it carefully. Generally, medicines prescribed by your doctor or bought over-the-counter from a pharmacist are licensed for use by the Medicines and Healthcare products Regulatory Agency (MHRA).

The licence (or marketing authorization) specifies the conditions and patient groups for which the medicine should be used, and how it should be given.

Patient Information Leaflets (PILs) supplied with medicines reflect the licensed uses. When a medicine is used beyond its licence, the information in the PIL may not be relevant to your circumstances.

In palliative care, medicines are commonly used for conditions or in ways that are not specified on the licence.

Your doctor will use medicines beyond the licence only when there is research and experience to back up such use.

Medicines used very successfully beyond the licence include some antidepressants and anti-epileptics (anti-seizure drugs) when given to relieve some types of pain.

Also, instead of injecting into a vein or muscle, medicines are often given subcutaneously (under the skin) because this is more comfortable and convenient.

If you would like more information, please ask your doctor or pharmacist.

Alternatively, contact:

Dr/Nurse .....

Hospital .....

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Tel .....

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**Box D** Recommendations of the Association for Palliative Medicine of Great Britain and Ireland and the British Pain Society<sup>17</sup>

**Use of medicines beyond (off-label) and without (unlicensed) Marketing Authorization (MA) in palliative care and pain medicine**

- 1 This statement should be seen as reflecting the views of a responsible body of opinion within the clinical specialties of palliative medicine and pain medicine
- 2 The use of medicines beyond and without a MA in palliative care and pain medicine practice is both necessary and common and should be seen as a legitimate aspect of clinical practice.
- 3 Organizations providing palliative care and pain medicine services should support therapeutic practices that are underpinned by evidence and advocated by a responsible body of professional opinion.
- 4 Health professionals involved in prescribing medicines beyond or without MA should select those medicines that offer the best balance of benefit against harm for any given patient.
- 5 Choice of treatment requires partnership between patients and health professionals, and informed consent should be obtained, whenever possible, before prescribing any medicine.
- 6 Patients should be offered accurate, clear and specific information that meets their needs about the use of medicines beyond or without a MA in accordance with professional regulatory body guidance. The information needs of carers and other health professionals involved in the care of the patient should also be considered and met as appropriate. The use of information cards or leaflets may help with this. It is often unnecessary to take additional steps when recommending medicines beyond or without MA.
- 7 Health professionals should inform, change and monitor their practice with regard to medicines beyond or without MA in the light of evidence from audit and published research.
- 8 The Department of Health should work with health professionals and the pharmaceutical industry to enable and encourage the extension of product licences where there is evidence of benefit in circumstances of defined clinical need.

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