UNLICENSED MEDICINAL PRODUCTS IN THE UK

A marketing authorisation is generally required for each medicinal product that is placed on the market in the UK. However, unlicensed medicinal products can be used under certain circumstances, one being to treat the particular clinical needs of individual patients that cannot be met by products with a marketing authorisation that are available in the UK. This is known variously as "named patient", "particular patient", "individual patient" or "compassionate use" supply. This note identifies EU and UK legislation, guidance and case law concerning such supply. This note also provides an overview of other permitted uses of unlicensed medicines.

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SCOPE OF THIS NOTE

In the UK, a medicinal product can generally only be placed on the market if particulars relating to its quality, safety and efficacy for its recommended use(s) meet the standards established by EU law and a marketing authorisation has been issued.

However, unlicensed medicinal products are frequently used to treat the particular clinical needs of individual patients that cannot be met by products with a marketing authorisation that are available in the UK. This is known variously as "named patient", "particular patient", "individual patient" or "compassionate use" supply. While this supply is not prohibited in the UK, it raises various regulatory issues.

This note examines:

- The EU regulatory framework relating to individual patient supply.
- UK regulation relating to individual patient supply.
- What constitutes "special needs".
- Prescribing unlicensed medicinal products.
- Manufacturing, wholesale dealing, importing, selling and supplying unlicensed products.
- Information for healthcare professionals, patient information and labelling.
- Advertising.
- Charging for supply.
- Pharmacovigilance.
- Additional circumstances in which unlicensed medicinal products may be supplied in the UK.
- The Early Access to Medicines Scheme.

EU REGULATORY FRAMEWORK RELATING TO INDIVIDUAL PATIENT SUPPLY

In general EU law requires the existence of a valid marketing authorisation, granted nationally or centrally by the European Commission, before a medicinal product can be placed on the market in a member state. However, Article 5.1 of *Directive 2001/83/EC relating to medicinal products for human use* (Medicinal Products Directive) creates a derogation:

> 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 health-care professional and for use by an individual patient under his direct personal responsibility.

Therefore, member states can develop national provisions to deal with the supply of unlicensed products, provided the legal framework established is consistent with the principle that the supply is required to meet the "special needs" of particular patients and the supply is not solicited. The exemption is narrowly drawn because the full safety and efficacy data will often not be available and the quality, safety and efficacy of these products may not have been independently assessed.

UK REGULATION OF INDIVIDUAL PATIENT SUPPLY

While the application of the EU regime in the UK may be subject to review in the context of its exit from the EU, the supply of unlicensed medicinal products for individual patients in the UK is currently governed by the *Human Medicines Regulations 2012 (SI 2012/1916) (2012 Regulations)*.

Regulation 46 of the *2012 Regulations* prohibits the sale or supply (or offer for sale or supply) of unauthorised medicinal products or otherwise than in accordance with the terms of a marketing authorisation. Exemptions to this requirement are set out in regulations 167 to 174 of the *2012 Regulations*. Regulation 167 implements Article 5.1 of the *Medicinal Products Directive* and therefore relates to individual patient supply. It reads as follows:

> The prohibitions in regulation 46 (requirement for authorisation) do not apply in relation to a medicinal product (a 'special medicinal product') if:
>
> a) the medicinal product is supplied in response to an unsolicited order;
>
> b) the medicinal product is manufactured and assembled in accordance with the specification of a person who is a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber;
>
> c) the medicinal product is for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient; and
>
> d) the following conditions are met.
>
> (Regulation 167(1), 2012 Regulations.)

The conditions referred to in regulation 167(d) are:

- The medicinal product is supplied to a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber, or for use under the supervision of a pharmacist in a registered pharmacy, a hospital or a health centre (*regulation 167(2), 2012 Regulations*). Supplementary prescribers include nurses, midwives, pharmacists, podiatrists, physiotherapists, diagnostic and therapeutic radiographers and optometrists, and can prescribe any medicine for any condition within their competence under an agreed clinical management plan agreed with an independent prescriber (*regulation 8, 2012 Regulations*).
- No advertisement relating to the medicinal product is published by any person (*regulation 167(3), 2012 Regulations*). See *Advertising* below.
- The manufacture and assembly of the medicinal product are carried out under such supervision and such precautions are taken to ensure that the product meets the specification of the doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber who requires it (*regulation 167(4), 2012 Regulations*).
- Written records of the manufacture or assembly of the medicinal product are maintained and are available to the licensing and enforcement authorities (*regulation 167(5), 2012 Regulations*).
- If the medicinal product is manufactured or assembled in the UK or imported into the UK from a country outside the EEA:
  - it is manufactured, assembled or imported by the holder of a manufacturer's "specials" licence granted by the Medicines and Healthcare products Regulatory Agency (MHRA) (*regulation 167(6)(a), 2012 Regulations*). The site will be inspected in the normal way to ensure compliance with good manufacturing practice (GMP). *The supply of unlicensed medicinal products ('specials'), MHRA guidance note 14* (Guidance Note 14) explains appropriate release arrangements and the focus of such inspections; or

- it is manufactured or assembled as an investigational medicinal product for clinical trial purposes (*regulation 167(6)(b), 2012 Regulations*).
- If the product is imported from a country within the EEA:
  - it is manufactured or assembled in that country by a person who is the holder of an appropriate specials manufacturing authorisation in relation to its manufacture or assembly in accordance with Article 40 of the *Medicinal Products Directive*, as implemented in that state. Provided the product is imported into the UK from an EEA member state in finished form, a wholesaler distribution authorisation will suffice for the importer (*regulation 167(7)(a), 2012 Regulations*); or
  - it is manufactured or assembled in that country for clinical trial purposes (*regulation 167(7)(b), 2012 Regulations*).
- If the product is distributed by way of wholesale dealing by a person who is not the manufacturing authorisation holder, the distributor holds a wholesaler distribution authorisation (*regulation 167(8), 2012 Regulations*).

RECORD KEEPING AND REPORTING OBLIGATIONS

Any person selling or supplying a unlicensed medicinal product in accordance with the provisions set out above must maintain, for a period of at least five years, records showing:

- The source from which, and the date on which, that person obtained the product.
- The person to whom, and the date on which, the sale or supply was made.
- The quantity of each sale or supply.
- The batch number of the batch of that product sold or supplied.
- Details of any suspected adverse reaction to the product sold or supplied of which they are aware. (This does not require a supplier to search the literature for reports concerning the substance.)

(Regulation 170(1), *2012 Regulations*.)

Regulation 170(2) and (3) require that person to notify the MHRA of any such suspected serious adverse reaction and to make available for inspection, on request, the records required to be kept under regulation 170(1).

These record keeping and reporting obligations are placed on any person selling or supplying "specials", not only manufacturers, importers and distributors, but also pharmacists, doctors, dentists, nurse independent prescribers, pharmacist independent prescribers and supplementary prescribers where appropriate.

WHAT CONSTITUTES "SPECIAL NEEDS"

The supply of an unlicensed product must be to "fulfil the special needs" of a patient (*regulation 167, 2012 Regulations*). This condition means that the exemption should only be available where there is no pharmaceutically equivalent product already authorised and on the market in the UK. This view has been endorsed in Guidance Note 14 and it also accords with the rationale underlying the Medicinal Product Directive, which requires only authorised medicinal products to be placed on the market, unless exceptional circumstances apply.

In Guidance Note 14, the MHRA confirms that the requirement for a "special need" relates to the special clinical needs of the individual patient and does not include reasons of cost, convenience or operational needs. This position derives from the decisions of the ECJ in *Commission v Poland (Case C-185/10) ECJ, 29 March 2012* and *Novartis Pharma GmbH v Apozyt GmbH (Case C-535/11) ECJ, 31 January 2013*, which concluded that, regardless of a cost comparison, there can be no "special needs" where an authorised product with the same active substance or substances, the same dosage (strength) and the same form as that which the doctor providing treatment considers that he must prescribe to treat his patients is available on the market.

The MHRA has taken a consistent approach, stating that supplying unlicensed products for reasons of cost, institutional need, convenience, preference for non-parallel imported products, more convenient presentation or longer shelf life is not acceptable; and these reasons do not amount to "special needs" (*see MHRA Inspectorate: Supply of unlicensed medicines when an equivalent licensed product becomes available*).

SPECIAL NEEDS ARISING FROM PRODUCT SHORTAGES

The MHRA accepts that where a licensed medicine is likely to be unavailable for a significant period (for example, because of a manufacturing interruption), a "special need" may exist, although this should be seen as a temporary measure and there should also be documented evidence of the shortage (for example, correspondence from the relevant marketing authorisation holder, notices in *The Pharmaceutical Journal* or confirmation from the MHRA or the Department of Health's commercial medicines unit). Special needs may also arise where a licensed product is discontinued for commercial reasons alone and there are no concerns as to patient safety.

A more difficult question arises where the product to be manufactured or imported differs in some way from the licensed version. The previous version of Guidance Note 14 stated that unlicensed products which are the "pharmaceutical equivalent" of available

licensed medicinal products will not be permitted, and that a medicinal product would be regarded as a "pharmaceutical equivalent" if all of the following criteria were met:

- It contained the same amount of the same active substance or, in the case of liquid dosage forms, the same concentration.
- It is in the same dosage form.
- It meets the same or comparable standards considered in the light of the clinical needs of the patient at the time of use of the product.

(*Guidance Note 14 (January 2008).*)

The term "pharmaceutical equivalent" and the above criteria were omitted from the most recent version of Guidance Note 14 (2014 version), but there is no reason to disregard these principles. As such a different formulation of an authorised substance (for example, one specifically formulated for children or the elderly, or those with an allergy to a particular excipient) might satisfy the principle of fulfilling special needs. Differences in strength are less likely to justify a special need and, in principle, the fact that a product equivalent to a product authorised in the UK is approved outside the UK for a different indication is irrelevant.

The 2014 version of Guidance Note 14 proposes the following decision hierarchy for determining when to use unlicensed medicinal products:

- Firstly, an unlicensed product should not be used where a licensed product is available within the UK to meet the patient's special need.
- Secondly, if a UK licensed product can meet the patient's clinical need, even "off-label", it should be used instead of an unlicensed product.
- Thirdly, if no UK licensed product meets the patient's special needs, then an imported medicinal product which is licensed in the country of origin should be considered.
- Fourthly, if none of the above options are available, a product that is completely unlicensed may have to be used, for example, "specials" manufactured in the UK, which are made in GMP inspected facilities.
- Lastly, the least acceptable products to be considered for use are those that are imported but unlicensed, and classed as medicines in the UK but not in the country of origin, as they may not be manufactured in accordance with pharmaceutical GMP.

PRESCRIBING UNLICENSED MEDICINAL PRODUCTS

Responsibility for deciding whether an individual patient has "special needs" which a licensed product cannot meet should be a matter for the healthcare professional responsible for the patient's care.

The circumstances under which a healthcare professional may prescribe unlicensed medicinal products are subject to guidance from the General Medical Council (GMC), an independent organisation in the UK responsible for managing the medical register and setting standards for doctors.

The GMC's 2013 guidance on prescribing unlicensed medicines states that healthcare professionals may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, they conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient (see *GMC: Good practice in prescribing and managing medicines and devices (2013)*). This may be necessary where:

- There is no suitably licensed medicine that will meet the patient's need. For example, if there is no licensed medicine applicable to the particular patient (such as where the patient is a child and the medicine is licensed only for adult patients).
- A medicine licensed in children would not meet the needs of a particular child patient, but a medicine licensed for the same condition or symptom in adults would.
- The dose specified for a licensed medicine would not meet the patient's need.
- The patient needs a medicine in a formulation that is not specified in an applicable licence.
- A suitably licensed medicine that would meet the patient's need is not available in the UK. For example, due to a temporary shortage in supply.
- The prescribing forms part of a properly approved research project.

When prescribing unlicensed medicines, healthcare professionals should:

- Be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy.
- Take responsibility for prescribing the medicine and for overseeing the patient's care, and any follow up treatment.
- Should keep clear records of all medicines prescribed and (if not following common practice) the reasons for prescribing an unlicensed medicine.

The GMC has clearly outlined its position on the prescription of both medicines with no UK licence and those being used off-label (see *GMC: Hot topic: Prescribing unlicensed medicines (November 2015)*). The GMC recognises that healthcare professionals are often worried about prescribing unlicensed medicines, but it confirms that its guidance does not include reference to any extra personal liability in relation to prescribing unlicensed medicines and that prescribing unlicensed medicines will not put healthcare professionals' registrations at risk any more than non-compliance

with other areas of practice covered by GMC guidance. The GMC expects healthcare professionals to be able to justify decisions and actions when prescribing, administering and managing medicines, regardless of whether they are licensed or unlicensed.

The GMC recommends that healthcare professionals give patients (or their parents or carers) sufficient information about the medicines being prescribed alongside the information provided with the product to allow them to make an informed decision on their use. Its 2013 guidance states that any healthcare professionals seeking to prescribe unlicensed medicines that are not routine or where suitably licensed alternatives are available, should explain this to the patient, and their reasons for doing so. However, it recognises that some medicines are routinely used outside the terms of their licence (for example, in treating children). In emergencies or where there is no realistic alternative treatment and such information is likely to cause distress, it may not be practical or necessary to draw attention to the unlicensed status of the product. In other cases, such as where the proposed prescription is supported by authoritative clinical guidance, it may be sufficient to describe in general terms that the medicine is not licensed for the proposed use or patient population.

ADDITIONAL CIRCUMSTANCES IN WHICH UNLICENSED MEDICINAL PRODUCTS MAY BE SUPPLIED IN THE UK

Regulations 168, 169 and 171 to 174 of the *2012 Regulations* consolidate various additional exemptions from the general requirement to hold a marketing authorisation, including those that were previously set out in separate legislation. These are summarised briefly below.

Regulation 168 sets out an exemption in certain circumstances for medicinal products not requiring a prescription for sale or supply, which are sold or supplied to a health care professional (as defined in regulation 8 of the *2012 Regulations*) exclusively for use by him in the course of his business for the purpose of administering it or causing it to be administered otherwise than by selling it.

Regulation 169 allows the holder of a non-orthodox practitioners authorisation to mix and assemble authorised medicinal products with other authorised medicinal products (or substances that are not medicinal products) without needing a marketing authorisation. The products used must be of general sales list status (that is, not prescription-only medicines). The person to whom the products are sold or supplied must be present and must make a request for exercise of judgement as to the treatment required. The product may not be advertised.

The record keeping and reporting obligations set out in regulation 170 also apply to any person selling or supplying a medicinal product in accordance with regulations 168 and 169.

Regulation 171 incorporates the exemption from marketing authorisation under the hospital exemption scheme established by Regulation (EC) No 1394/2007 on advanced therapy medicinal products (ATMPs). ATMPs are excluded from the scope of the Directive to the extent that they are:

- Prepared on a non-routine basis according to specific quality standards equivalent to those provided for centrally authorised ATMPs.
- Used in a hospital under the exclusive professional responsibility of a doctor, in order to comply with an individual medical prescription for a custom custom-made product for an individual patient.

This exemption was included in Regulation (EC) 1394/2007 in recognition of the small scale and developmental nature of activity carried out in some hospitals, which necessitated flexibility in the regulatory requirements.

While legally distinct, there are similarities between the hospital exemption under regulation 171 of the *2012 Regulations* and the individual patient supply arrangements under regulation 167, as the products under both schemes are excluded from the requirement for marketing authorisation. The individual patient supply arrangements under regulation 167 are, in principle, available for ATMPs as for any other category of medicinal product. However, there are a number of differences between the two schemes. Exempt ATMPs must be prepared in the UK for use in a UK hospital under the responsibility of a doctor. Products supplied under regulation 167, however, may be manufactured within or outside the UK and may be supplied for use under the supervision of a pharmacist in a pharmacy, hospital or health centre.

Exempt ATMPs must be prepared on a non-routine basis, while products for individual patient supplies need only be to fulfil the special needs of that patient. The meaning of "non-routine preparation" is determined with reference to the scale and frequency of preparation; special needs is generally interpreted to mean the absence of an equivalent licensed product. Provided this requirement is met, individual patient supplies may, in contrast to ATMPs, be prepared on a routine, long-term basis. Further differences between the two schemes exist in relation to good manufacturing practice, traceability and patient information.

Regulation 172 clarifies that the holder of a parallel import licence does not need to obtain a marketing authorisation to place the product to which the licence relates on the market, or to sell or supply (or offer for sale or supply) the product to which the parallel import licence relates, provided these activities are carried out in accordance with the terms of the licence.

Regulation 173 contains an exemption for radiopharmaceuticals prepared at the time of administration from an authorised kit, generator or precursor in relation to which there is a marketing authorisation in force, subject to certain conditions.

Regulation 174 contains an exemption for the sale or supply of products that are authorised by the MHRA on a temporary basis in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents, or nuclear radiation, which may cause harm to human beings.

EARLY ACCESS TO MEDICINES SCHEME

In April 2014 the UK government introduced the Early Access to Medicines Scheme (EAMS), a scheme intended to allow patients to access innovative unlicensed or off-label medicines used in treating, diagnosing or preventing life-threatening, chronic or seriously debilitating conditions with a high unmet need up to a year earlier than the current marketing authorisation procedures permit. EAMS is a voluntary and non-statutory scheme that runs in parallel with the existing UK and EU licensing procedures.

EAMS is aimed at products that have completed Phase III trials, but may be applied to those that have completed Phase II trials in exceptional circumstances. There must be sufficient quality, safety and efficacy data available to show that the risk/benefit profile of the product is positive, and that the medicine represents a significant advance in the treatment of an unmet need. Companies with the appropriate data may apply to MHRA for an EAMS scientific opinion. Where the evidence is sufficiently compelling, the MHRA will publish a public assessment report and the EAMS treatment protocol intended to support prescribers in deciding whether to use the medicine on an unlicensed or off-label basis.

Even if a positive EAMS opinion is received, the rules on promotion of unlicensed medicinal products continue to apply, and companies are not permitted to draw the attention of prescribers to products that have received such opinions. Before the launch of EAMS, the UK government had suggested that professional groups, such as Royal Colleges, could be instrumental in ensuring prescribers were made aware of such developments. However, this does not seem to have happened. It seems that the advertising rules under EAMS may be stricter than for the supply of other unlicensed medicinal products, as companies may be unable even to provide factual information or press releases about opinions issued under the scheme.

For more information on the EAMS application process, see *MHRA: Apply for the early access to medicines scheme (EAMS)*.