

UNLICENSED MEDICINAL PRODUCTS IN THE UK

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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 special 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.

MANUFACTURING, WHOLESALE DEALING, IMPORTING, SELLING AND SUPPLYING UNLICENSED PRODUCTS

Article 5.1 of the *Medicinal Products Directive* and the corresponding provisions of the 2012 provide exemptions from the requirement to hold a marketing authorisation, but companies involved in the supply chain for unlicensed medicinal products are likely to require additional licences in relation to their activities.

MANUFACTURE

Those involved in the manufacture or assembly of a medicinal product must hold a manufacturer's licence (*regulation 17(1), 2012 Regulations*). Regulation 46(4) of the 2012 Regulations prohibits the manufacture of a medicinal product unless that product has a marketing authorisation or is exempt from the marketing authorisation requirement. The manufacturer or assembler in the UK of an unlicensed product for individual patient supply must hold a particular type of manufacturer's licence (a manufacturer's "specials" licence (*regulation 167(6), 2012 Regulations*)).

The quality controls for manufacture of licensed medicines on a large scale may not always be appropriate for the manufacture of unlicensed products, which may vary from sporadic low volumes to regular requirements for large volumes of product. As such, the MHRA's GMP Inspectorate has published *MHRA Guidance for Specials manufacturers*, which is

detailed guidance in "Q&A" format for Manufacturing Specials licence holders, on the interpretation of the relevant GMP requirements for unlicensed medicinal products, to reflect the scale and nature of production of unlicensed medicinal products.

The guidance states that manufacturers should formulate products in line with the healthcare professional's order, unless the order does not adequately describe the formulation, in which case it may be determined by the manufacturer, and (if necessary) confirmed with the customer. Product formulations should be derived by appropriately qualified and experienced personnel and independently checked against the requirements of the order and the intended route of administration. Where a British Pharmacopoeia (BP) monograph for a product exists, the sale or supply of that product in the UK must comply with the monograph. Monographs define quality standards for medicines in terms of analytical methods and assessment.

Manufacturers should also have systems in place to ensure that medicines are not supplied where a licensed alternative exists. These checks should take place where products are manufactured in response to a specific order, and if stock items are supplied the company should monitor marketing authorisation approvals to check that no licensed alternatives have become available. There is currently no published definitive list of all medicines licensed for use in the UK, and so any checks should include at least:

- The NHS drug tariff.
- The Electronic Medicines Compendium.
- The British National Formulary.

Additional exemptions in section 10 of the *Medicines Act 1968* allow pharmacies to manufacture unlicensed medicinal products without the need for a manufacturing licence under certain circumstances:

- For individual patients in accordance with prescriptions.
- For the purposes of preparing a stock of medicinal products with a view to preparing or dispensing a medicinal product in accordance with a prescription.

The Department of Health proposed changes to restrict these exemptions following the July 2015 judgment in *Abcur AB v Apoteket Farmaci AB and other (Joined Cases C-544/13 and C-545/13) ECJ, 16 July 2015*.

The cases related to the ability of Apoteket, a state-owned company in Sweden, to produce unlicensed preparations of methadone and noradrenaline when licensed preparations were available on the Swedish market. Apoteket relied on Article 3 of the *Medicinal Products Directive*, which describes products that fall outside the scope of the Directive, focussing on points 1 and 2 of Article 3, which state:

This Directive shall not apply to:

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).
2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the official formula).

In its judgment, the court clarified that these conditions must both be met for the exemption to apply.

Therefore, in a March 2016 consultation document the Department proposed repealing section 10 of the *Medicines Act 1968* and addressing the pharmacists' exemption in the *2012 Regulations* to ensure consistency with the ECJ's judgment. However, on 7 June 2016 the Department stated that it was delaying any changes to allow more detailed exploration of the issue with relevant stakeholders. Amendments to pharmacies' ability to manufacture unlicensed products without a manufacturing licence may, therefore, be expected.

WHOLESALE DEALING AND IMPORTING UNLICENSED MEDICINAL PRODUCTS

Regulation 167 of the *2012 Regulations* confirms that if an unlicensed medicinal product is distributed by way of wholesale distribution then the relevant distributor must hold a corresponding wholesale distribution authorisation granted pursuant to regulation 18(1) of *2012 Regulations*. Wholesale distribution includes imports from an EEA member state; where imports originate from a country outside the EEA then a manufacturer's licence will be required.

Schedule 4 to the *2012 Regulations* includes standard provisions for manufacturer's licences and wholesale dealer's licences relating to unlicensed medicinal products (that is, products to which regulation 167 of the *2012 Regulations*, or equivalent legislation in other EEA countries, applies). Imports of special medicinal products are only permitted where the following conditions are complied with:

- At least 28 days before each importation, the licence holder must give written notice to the "licensing authority", together with certain specified details relating to the product, the quantity to be imported and the manufacturer/assembler/supplier. In practice, notice is given to the MHRA, which acts on behalf of the licensing authority.
- If, within 28 days of acknowledgement of receipt of the notice, the MHRA notifies the licence holder that the product should not be imported, the licence holder must comply. If instead it receives notification from MHRA that the product may be imported, or if MHRA does not object within 28 days of their acknowledgement of receipt of the notice, then the licence holder may proceed.

- Where it sells or supplies special medicinal products the licence holder must keep records of the batch number of the product from which the sale or supply was made, and of any adverse reaction of which it becomes aware.
- The licence holder may not import on any one occasion more product than is sufficient for 25 single administrations or for 25 courses of up to three months treatment. It may not import more than the quantity stated in its notice to the MHRA, although there is no rule against multiple, sequential, notifications.
- The licence holder must not publish any advertisement, catalogue or circular, or make any representations, relating to the imported product. (In the context of price lists without product claims it would appear that this prohibition needs to be interpreted in the light of the definition of advertising in regulation 7 of the *2012 Regulations*, discussed further below.)
- The licence holder must inform the MHRA immediately of any matter which might reasonably cause the MHRA to believe that the product can no longer be regarded as safe or of satisfactory quality, and cease importation or supply, if directed to do so by the MHRA.

(Paragraph 22 and 34-41, Schedule 4, *2012 Regulations*.)

It is clear from the above summary that, currently, imported products are subject to greater regulatory scrutiny than products manufactured in the UK. Unlicensed medicinal products made in the UK must meet various conditions, but there is no requirement for each supply to be notified to the MHRA. However, where the unlicensed product is imported from another country there is a notification requirement, and so in practice the ability of the MHRA to question whether a "special need" exists is much greater where the product is imported than where it is procured from a UK manufacturing "specials" licence holder. In 2008 the MHRA published an informal consultation paper on the review of the regulation of unlicensed medicines which suggested that the national rules would be reviewed, but to date nothing has come of this review.

SALE AND SUPPLY OF UNLICENSED PRODUCTS

UK licensed manufacturers and wholesale dealers may only sell or supply unlicensed medicinal products to:

- The holder of a wholesale dealer's licence relating to those products (or an equivalent authorisation granted by the competent authorities of another EEA country).
- A person entitled to supply medicinal products in circumstances corresponding to retail sale (for example, a pharmacist).
- A person who may lawfully administer those products.

UK licensed manufacturers and wholesale dealers should take reasonable steps to establish that persons supplied satisfy the UK regulatory requirements concerning individual patient supply. In Guidance Note 14 the MHRA states that documentary evidence of the special need for the unlicensed product should be obtained by manufacturers, importers or distributors and that this evidence should be made available on request to the MHRA. This evidence could be a prescriber's letter confirming professional status and the nature of the special need of the individual patient concerned, and making clear any licensed alternatives are not clinically appropriate. Alternatively a fully documented audit trail through the supply chain confirming special need may be acceptable. New letters from prescribers are not required for every supply if, for example, a group of individual patients have a continuing need for the products in question. There is no legal requirement for the individual patients' names to be supplied. Evidence covering groups of patients, such as those who cannot swallow, may be acceptable, as may requirements for a lactose or sugar free formulation.

All of the relevant parties involved in the supply of unlicensed products should be aware of the status of the products in question. The absence of a marketing authorisation number on the packaging should be sufficient to make it clear that the products are unlicensed, but if the prescriber may not see the product packaging (for example, where the product is ordered by a hospital pharmacist and administered by a nurse) then the pharmacist should ensure that the prescriber is aware of the status of the product before it is ordered and administered.

INFORMATION FOR HEALTHCARE PROFESSIONALS, PATIENT INFORMATION AND LABELLING

The MHRA acknowledges in its Q&A guidance for specials manufacturers that, as a matter of good practice, where appropriate, unlicensed products should include an information sheet for healthcare professionals. The European Commission has also endorsed the supply of non-promotional information sheets explaining what is known about the product.

Where unlicensed products are imported into the UK, there is no regulatory requirement for any foreign patient information leaflet (PIL) to be translated into English. In certain situations, this may pose a dilemma. For example, the determination of whether patient safety is best served by the supply of either:

- A medicine that is not manufactured under EU or GMP standards, but is accompanied by a PIL in English.
- A medicine that meets EU standards, but only has a PIL in another language.

While there are some circumstances where the inclusion of a PIL may not be possible (such as where there is an urgent clinical need), it is certainly desirable for suppliers to provide some information about the product for the patient.

Leaflets have been developed for some well-established unlicensed medicinal products for the benefit of patients, and the MHRA views this as best practice, although any such guidance should be approved by an appropriately qualified medical professional with knowledge of the use of the product for the patient(s) in question.

The MHRA Q&A guidance also states that unlicensed medicinal products should be labelled in accordance with the BP general monograph for unlicensed medicinal products (part II and V), and in accordance with the general monograph for the specific dosage form. The BP notes that labelling of medicines is a critical contributor to patient safety, but confirms that there are no specific legal requirements for labelling. However, it states that as a matter of best practice the information which should appear on the label includes:

- The common name of the product.
- A statement of the active ingredients stated quantitatively and qualitatively per dosage unit or for a given volume or weight.
- Route of administration.
- Instructions for use including any special warnings.

Excipients of known effect or all excipients for injectable, topical (including inhalations), ophthalmic should also be included on the label. The general monograph for "Substances for Pharmaceutical Use" also states that, where appropriate, the name and concentration of any excipient should be included on the label.

Imported unlicensed medicinal products are outside the scope of the BP general monograph on unlicensed medicinal products. However where an individual monograph exists for an imported unlicensed medicinal product then the product must comply.

Unlicensed products should not be labelled "prescription only medicine" or "POM". While they do not appear on the list of products subject to general sale, and cannot be sold over-the-counter in pharmacies, the MHRA's view is that this does not render them POM products. POM status is recorded via licensed products' marketing authorisations; unlicensed medicinal products do not have a marketing authorisation and so formally cannot be POM products. It has been proposed that products should be labelled as "unlicensed in the UK" instead. While such labelling is desirable on the grounds of transparency, there is a concern that it may erroneously convey the impression that the product does not meet any regulatory standards and may worry patients unnecessarily.

If the product is manufactured in the UK under a manufacturer's "specials" licence then the licence number should also be included on the label.

ADVERTISING

No advertisement may be published to promote the prescription, supply, sale or use of special medicinal products (*regulation 167(3), 2012 Regulations*). Sale or supply must be in response to an unsolicited order from the healthcare professional. "Advertisement" is defined broadly in regulation 7 of the *2012 Regulations*, but the definition expressly excludes reference material and announcements of a factual and informative nature, including:

- Material relating to changes to a medicinal product's package or package leaflet.
- Adverse reaction warnings.
- Trade catalogues.
- Price lists, provided that no product claim is made.

A supplier may also respond to unprompted specific questions about a medicinal product.

Price lists were once seen as prohibited advertisements, but following the decision of the ECJ in *Ludwigs-Apotheke (Case C-143/06), European Court Reports 2007 I-09623*, the restriction was deleted and, accordingly, the circulation of price lists of unlicensed products is no longer prohibited, provided they contain only limited information. The MHRA advises that price lists may be sent out at reasonable intervals or in response to an enquiry, but should typically consist of a basic line listing with the drug name and reference number, dosage form, strength, pack size and price (*Guidance Note 14*). Product claims may not be included.

In addition to the specific prohibitions in relation to unlicensed medicinal products, companies should note the more general provisions relating to advertising. It is a criminal offence to:

- Issue an advertisement for a relevant medicinal product in respect of which there is no marketing authorisation in force (*regulation 279, 2012 Regulations*).
- Issue an advertisement that does not comply with the particulars listed in the summary of product characteristics (that is, advertising an off-label usage) (*regulation 280, 2012 Regulations*).

Corresponding restrictions on the use of promotional materials also appear in the *Code of Practice of the Association of the British Pharmaceutical Industry (ABPI)*.

The MHRA has, since December 2003, published on its website the results of its scrutiny of questionable advertising. Usually, the MHRA warns the person concerned as to their obligations and requires an immediate end to the promotion in question. Prosecution is possible, but rare.

CHARGING FOR SUPPLY

The 2012 Regulations do not place any restrictions on companies charging for the supply of unlicensed medicinal products, and historically there were no other restrictions on pricing or pharmacies' ability to seek reimbursement for unlicensed medicinal products under the NHS.

However, concerns that some pharmacies were making excess margins on unlicensed medicinal products led to the introduction of a new Part VIII B of the Drug Tariff (see *NHS: Electronic Drug Tariff: Arrangements for payment for Specials and Imported Unlicensed Medicines*). As at August 2016 this set limits on prices of 250 high-cost, high-volume unlicensed medicinal products prescribed commonly and supplied on NHS prescription, using sales and volume data from suppliers (see *NHS: Part VIII B: August 2016*).

In addition, the pricing of prescriptions for medicinal products unlisted in the Drug Tariff is also restricted, depending on how the product was sourced. Prescriptions of imported unlicensed medicinal products or products sourced in the UK from manufacturers holding a manufacturer's "specials" licence, that are not listed individually in Part VIII B, attract reimbursement at the price endorsed on the prescription, and this must be the invoice price less any discount or rebate given to the pharmacist and linked to the procurement of the product. Where products are manufactured by the pharmacist under section 10 of the *Medicines Act 1968*, the pharmacist will be paid the cost of the ingredients used to manufacture the product. Additional fees for "out of pocket expenses" (for example, carriage) can be claimed, pursuant to clause 12 of the Drug Tariff, if the prescription is appropriately endorsed.

Pharmacies must keep records of:

- The source of the special or imported unlicensed product.
- The person to whom and the date on which the special or imported unlicensed product was sold or supplied.
- The prescriber's details.
- The quantity of each sale or supply.
- The batch number of the special.

These records must be made available for inspection by the MHRA. For unlisted unlicensed medicinal products they should also stamp, date, initial and endorse the Certificate of Analysis or Certificate of Conformity (if available) with the invoice price less discount and prescriber's details and provide these to the NHS in order for it to match expenditure to the special supplied.

PHARMACOVIGILANCE

UK manufacturers and importers of unlicensed medicinal products are obliged to communicate all suspected adverse drug reactions (ADRs) to the MHRA (regulation 170, *2012 Regulations*). Manufacturers should report a suspected ADR immediately and in no case later than 15 calendar days from receipt, stating that the product is unlicensed (*Guidance Note 14*).

Reports should be submitted electronically using the ICH-E2B standard electronic report and via the EudraVigilance European Gateway. Prescribers and pharmacists supplying “specials” should report ADRs using a Yellow Card form or an electronic Yellow Card, stating the manufacturer and indicating that the product is unlicensed.

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-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 \(EAMS\)](#).

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