The supply of unlicensed medicinal products ("specials")

MHRA Guidance Note 14

Medicines and Healthcare Products Regulatory Agency

The supply of unlicensed medicinal products (“specials”)

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1 Introduction

1.1 MHRA is responsible for ensuring that medicines and medical devices work, are safe and of an appropriate quality. MHRA's primary aim is to safeguard public health through a system of regulation. Pharmaceutical manufacturers and distributors operating in the UK marketplace are subject to a system of licensing and inspection, which ensures that licensed medicinal products conform to internationally-agreed standards, and that those medicines are manufactured, stored and distributed in compliance with the required regulatory standards.

1.2 The regulation of medicines on the UK market is undertaken by MHRA in accordance with the Human Medicines Regulations 2012 (SI 2012/1916).

1.3 This Guidance Note provides advice on the manufacture, importation, distribution and supply of unlicensed medicinal products for human use (commonly described as "specials") which have been specially manufactured or imported to the order of a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber for the treatment of individual patients.

1.4 Unless exempt, a medicinal product must be the subject of a marketing authorisation or product licence before being placed on the market. Regulation 167 of the Human Medicines Regulations 2012 (see Appendix 1) provides an exemption from the need for a marketing authorisation for a medicinal product which is supplied:

- in response to an unsolicited order;
- 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;
- for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient; and meets the conditions specified in regulation 167(2)-(8).

1.5 In the interest of public health the exemption is narrowly drawn because these products, unlike licensed medicinal products, may not have been assessed by the Licensing Authority against the criteria of safety, quality and efficacy.

1.6 The exemption and this guidance does not apply to other unlicensed medicinal products, for example:

- unlicensed herbal remedies supplied under regulation 3(6) of the Human Medicines Regulations 2012;
- unlicensed homoeopathic medicines (prepared in a pharmacy);
- investigational medicinal products;
- intermediate products intended for further processing by an authorised manufacturer;
- medicinal products for export to countries outside of the European Economic Area;
- products prepared in a pharmacy under regulation 4 of the Human Medicines Regulations 2012;

- products prepared by a doctor or dentist under regulation 3(5) of the Human Medicines Regulations 2012;
- repackaging licensed products for their authorised use;
- reconstituted IV additives and CIVAS products (prepared in a pharmacy);
- products supplied for compassionate use in accordance with Article 83 of Regulation (EC) 726/2004 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac058007e691;
- temporarily-authorised medicinal products supplied in response to the spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm (in accordance with Article 5(2) of Directive 2001/83/EC).

1.7 The manufacture and distribution of veterinary unlicensed medicinal products for animal use is subject to separate legislation. Further advice should be sought from the Veterinary Medicines Directorate (VMD) of DEFRA.

1.8 The Licensing Authority, for the purposes of the Human Medicines Regulations 2012 and this guidance, refers to the UK Ministers[1] designated by the Regulations, acting either alone or jointly. MHRA is the Government body set up to discharge the responsibilities of the Licensing Authority, under powers delegated by those Ministers.

2 Special needs

2.1 Regulation 167 of the Human Medicines Regulations 2012 sets out the exemption from the requirement for a medicinal product, placed on the market in the UK to hold a marketing authorisation. This exemption flows from Article 5(1) of Directive 2001/83/EC, which states:

'A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility.'

2.2 An unlicensed medicinal product may only be supplied in order to meet the special needs of an individual patient. An unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient. Responsibility for deciding whether an individual patient has "special needs" which a licensed product cannot meet should be a matter for the doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber responsible for the patient's care. Examples of "special needs" include an intolerance or allergy to a particular ingredient, or an inability to ingest solid oral dosage forms. These examples are not exhaustive.

[1] The Secretary of State and the Minister for Health, Social Services and Public Safety.

2.3 The requirement for a “special need” relates to the special **clinical** needs of the individual patient. It does not include reasons of cost, convenience or operational needs (see Section 10 of this guide). Anyone supplying an unlicensed medicinal product, where an equivalent licensed medicinal product is available must be satisfied as to the existence of a special need for the unlicensed medicinal product. MHRA expects that documentary evidence of this special need should be obtained by manufacturers, importers or distributors and that this evidence should be made available on request of the Licensing Authority. This may take the form of a prescriber’s letter, however an alternative fully documented audit trail through the supply chain confirming special need may be acceptable.

2.4 Although MHRA does not recommend “off-label” (outside the licensed indications) use of products, if a UK licensed product can meet the clinical need, even off-label, it should be used instead of an unlicensed product (see Appendix 2).

2.5 A licensed medicinal product obtainable from normal distribution channels in a reasonable time should be considered available for use. If a licensed product becomes unavailable, it may be necessary for an unlicensed equivalent to be supplied. This should be seen as a temporary expedient and should not be taken as justification for long term supply. Supply in these circumstances should cease as soon as is practicable, following re-instatement of the licensed product.

2.6 A “special” may only be supplied to third parties if all of the following apply:

- there is an unsolicited order;
- the product is manufactured and assembled in accordance with the specification of a person who is adoctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber registered in the UK;
- the product is for use by a patient for whose treatment that person is directly responsible in order to fulfill the special needs of that patient; and
- the product is manufactured and supplied under specific conditions (see Sections 3 to10).

3 Persons authorised to procure “specials” in the UK

3.1 They are:

(a) doctors or dentists registered in the UK;
(b) supplementary prescribers (e.g. an appropriately qualified nurse or pharmacist);
(c) nurse independent prescribers or pharmacist independent prescribers;
(d) pharmacists in hospitals, health centres or registered pharmacies;
(e) wholesale dealers licensed for supply to the order of any of the above;
(f) manufacturers licensed for import for supply to the order of any of the above.

3.2 UK licensed manufacturers and wholesale dealers should take reasonable steps to establish that persons supplied satisfy the requirements of regulation 167, and intend to use the product in a way which falls within the specified terms. This could be achieved, for example, by the person ordering the “special” confirming their professional status

and the nature of the special need of the individual patient concerned, making clear that where a licensed alternative is available, why that is not clinically appropriate. There is no legal requirement for the individual patient's name to be supplied (see Appendix 1).

3.3 All involved in the supply chain should be aware of the unlicensed status of the product. It should be clear from the product's packaging that the product is unlicensed because there will be no marketing authorisation/product licence number on it. However, a prescriber may not have sight of the product, for example, where it is ordered by a hospital pharmacist and administered by a nurse. In such cases the pharmacist should ensure before the product is ordered and administered that the prescriber is fully aware of the unlicensed status of the product. Healthcare providers (such as Health Boards, NHS Hospital Trusts, Clinical Commissioning Groups and independent hospitals) may have policies on the commissioning and use of unlicensed medicines.

4 Manufacture and assembly in the UK

4.1 The manufacturer or assembler of "specials" must hold a Manufacturer's "Specials" Licence granted by the Licensing Authority. The licence should be applied for in the usual way (subject to the usual application procedures and conditions, see MHRA Guidance Note 5, Notes for applicants and holders of Manufacturer's Licences). The manufacturing/assembly site and its operations will be inspected for compliance with Good Manufacturing Practice (GMP) and the conditions of the licence. These require that manufacture or assembly is carried out under the supervision of appropriately qualified staff, including a named quality controller and production manager, who are acceptable to the Licensing Authority. However, a Qualified Person (QP) is not required to be named on a Manufacturer's "Specials" Licence for release of a finished unlicensed product.

4.2 Release of "specials" should be by the quality controller or a nominated deputy. Adequate precautions should be taken to ensure that the product is of the quality required for its intended purpose and that it complies with any standards described in relevant pharmacopoeial monographs. Written records of manufacture/assembly and supply must be kept for five years and be made available to the Licensing Authority on request.

4.3 When inspecting a "specials" manufacturing site, in addition to confirming compliance with GMP and the Human Medicines Regulations 2012, an Inspector will also take account of product specifications, labelling, stability data and justification for expiry dating.

4.4 The licence holder must demonstrate compliance with the European Commission's 'Notes for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products' and future updates, in accordance with The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [SI 2003/1680]. See MHRA's guidance: Minimising the risk of Transmission of Transmissible Spongiform Encephalopathies via Unlicensed Medicinal Products for Human Use, available from MHRA's website www.mhra.gov.uk

4.5 A holder of a Manufacturer's "Specials" Licence may also be a registered pharmacy supplying unlicensed medicinal products prepared under the exemption provided by regulation 4 of The Human Medicines Regulations 2012. Under these circumstances, the labelling of products prepared under regulation 4, and any documentation associated with them, should not make reference to the Manufacturer's "Specials" Licence or number.

4.6 For guidance on labelling of unlicensed medicinal products manufactured by the holder of a Manufacturer's Licence, please refer to the relevant monographs of the British Pharmacopoeia[2].

5 Importation into the UK

5.1 The importer of an unlicensed medicinal product (a "special") into the UK must hold;

(a) a Wholesale Dealer's Licence (WDA (H)) if the product is to be imported from an EEA member state i.e. the EU plus Norway, Iceland and Liechtenstein, or
(b) a Manufacturer's "Specials" Licence if the product is to be imported from a third country i.e. a non-EEA country.

5.2 The holder of the Wholesale Dealer's Licence or Manufacturer's "Specials" Licence, must comply with certain obligations in relation to the import of an unlicensed medicinal product, which are set out in Schedule 4 of the Human Medicines Regulations 2012. Specifically they require that where the licence relates to a "special" the licence holder shall only import such products —

(1) (a) in response to an order which satisfies the requirements of regulation 167 of the Human Medicines Regulations 2012; and

(b) where the conditions set out in sub-paragraphs (2) to (8) are complied with.

(2) A notification to MHRA must be given at least 28 days before the date of the intended import stating:

(a) The name of the product, which may be the brand name, common name or scientific name under which it is to be sold or supplied.

(b) Any trademark or name of the manufacturer.

(c) The International Non-proprietary Name (INN), British Approved Name (BAN) or other monograph, scientific name or description of the true nature of each of the constituents. The use of British English names and spellings is preferred e.g. Adrenaline rather than Epinephrine, Erythromycin rather than Erythromycina.

(d) The quantity to be imported which may be 25 individual doses or a quantity that must not exceed that required for 25 courses of no more than 3 months. It

[2] British Pharmacopoeia Volume III – Formulated Preparations: General Monographs Unlicensed Medicines
British Pharmacopoeia Volume V – Supplementary Chapters – SC V Unlicensed Medicines SC V Unlicensed Medicines

should be noted, by example, that if a patient only ever receives a 2 week course in any 3 months this would equate to twenty-five 2 week courses.

(e) The name and address of the manufacturer or assembler of the medical product, or the name and address of the supplier if not the manufacturer or assembler.

(3) The special medicinal product must not be imported if the Licensing Authority issues an objection to import within 28 days of their acknowledgment of the notification of intent to import.

(4) The Licensing Authority may choose to permit import before 28 days from the date of their acknowledgment. This is usually only used in the case of immediate import of medicines for life threatening or immediately injurious clinical emergencies.

(5) Records required in addition to other provisions of licences are:

(a) The batch number of the product supplied.

(b) Details of any adverse reactions to the product supplied of which the licence holder becomes aware.

(6) The licence holder must not import more than the quantity notified to the Licensing Authority.

(7) The licence holder must not publish any advertisement, catalogue or circular relating to a special medicinal product or make any representations in respect of that product. Announcements of a factual and informative nature, such as a price list, may be permitted under certain circumstances. See Section 7 for further information.

(8) The licence holder must inform the Licensing Authority immediately of any matter coming to their attention which may mean that an unlicensed medicine they have imported may not be safe or of adequate quality for administration to humans.

(9) The licence holder must cease import or supply of a special medicinal product or class of products from a specified date if so instructed by the Licensing Authority.

5.3 The licence holder shall take all reasonable precautions and exercise all due diligence to ensure that any information he provides to the Licensing Authority which is relevant to an evaluation of the safety, quality or efficacy of any medicinal product for human use which he imports from a third country, handles, stores or distributes is not false or misleading in a material particular.

5.4 The licence holder must demonstrate compliance with the European Commission's 'Notes for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products' and future updates, in accordance with, The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [SI 2003/1680]. See MHRA's guidance: Minimising the risk of Transmission of Transmissible Spongiform Encephalopathies via Unlicensed Medicinal Products for Human Use, available from MHRA's website www.mhra.gov.uk

6 Distribution

6.1 Distribution by wholesale dealing must be through licensed wholesale dealers, subject to the usual application procedures and conditions, and appropriate records must be kept.

6.2 Directive 2001/83/EC defines wholesale distribution of medicinal products as: 'All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned.'

6.3 The holder of a Wholesale Dealer's Licence (WDA(H)), must only supply unlicensed medicinal products to:

- the holder of a Wholesale Dealer's Licence relating to those products;
- the holder of an authorisation granted by the competent authority of another EEA State authorising the supply of those products by way of wholesale dealing;
- any person who may lawfully supply medicinal products in circumstances corresponding to retail sale, or
- any person who may lawfully administer those products.

6.4 The holder of a Manufacturer's "Specials" Licence must comply with these requirements in order to distribute the unlicensed medicines that they have manufactured or imported as if they were the holder of a Wholesale Dealer's Licence.

7 Advertising

7.1 A "specials" manufacturer, importer or wholesaler may advertise the service he provides but particular "specials" must not be advertised as provided by condition B of regulation 167 of the Human Medicines Regulations 2012. He may, however, provide factual responses to requests for information on specific "specials" or the range of products he is able to supply.

7.2 "Advertisement" is defined in regulation 7 of the Human Medicines Regulations 2012 as "anything designed to promote the prescription, supply, sale or use" of a "special" and includes, in particular, the following activities—

- door-to-door canvassing;
- visits by medical sales representatives to persons qualified to prescribe or supply medicinal products;
- the supply of samples;
- the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except where the intrinsic value of such inducements is minimal;

- the sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products; and
- the sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products, including the payment of their travelling and accommodation expenses in that connection.

7.3 "Advertisement" does not include 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, and
- price lists,

provided that no product claim is made.

7.4 Paragraphs 22(7) and 40 of Schedule 4 of the Human Medicines Regulations 2012 preclude a "specials" manufacturer, importer or wholesaler from publishing a catalogue or circular. However, provided no product claim is made, a trade catalogue or circular can be sent to an authorised healthcare professional where it is relevant to respond to an unsolicited request for information on the range of products supplied.

7.5 Additionally, a "specials" manufacturer, importer or wholesaler may issue a price list to authorised healthcare professionals to whom the price of "specials" may be relevant, such as potential customers and budget managers. Price lists can be sent out at reasonable intervals or in response to an enquiry.

7.6 A price list would typically consist of a basic line listing providing the following information:

- reference number;
- drug name (British Approved Name or equivalent);
- dosage form;
- strength;
- pack size; and
- price.

No product claims may be included.

7.7 This advice takes into account the decision of the European Court of Justice in *Ref: C-143/06 Ludwigs-Apotheke München Internationale Apotheke v Juers Pharma Import-Export* GmbH (see Section 10).

7.8 For further advice on the prohibition of advertising unlicensed medicines see Section 4.2 of the Blue Guide 'Advertising and Promotion of Medicines in the UK. This is available at the following link:

http://www.mhra.gov.uk/Howweregulate/Medicines/Advertisingofmedicines/BlueGuide/index.htm

8 Obligations on persons who sell or supply

8.1 Regulation 170 of The Human Medicines Regulations 2012 lays down the obligations on persons who sell or supply “specials”.

8.2 Any person selling or supplying a “special” must:

(a) keep the following records for at least 5 years:

- the source from which and the date on which the person obtained the product;
- the person to whom and the date on which the sale or supply was made;
- the quantity of the sale or supply;
- the batch number of the batch of that product from which the sale or supply was made; and
- details of any suspected adverse reaction to the product so sold or supplied of which the person is aware or subsequently becomes aware.

(b) make these records available for inspection by the Licensing Authority;

(c) report serious suspected adverse drug reactions (ADRs) to MHRA;

- manufacturers should report the suspected ADR immediately and in no case later than 15 calendar days from receipt, stating that the product is unlicensed. It is a mandatory requirement to electronically report suspected ADRs. The ICH-E2B international standard electronic report should be used and the report should be electronically submitted via the EudraVigilance European Gateway (see MHRA or EMA websites for more details).
- prescribers or pharmacists supplying the “special” should report using a Yellow Card form or an electronic Yellow Card (found at http://www.mhra.gov.uk/yellowcard), stating the manufacturer and indicating that the product is unlicensed.

8.3 These 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.

9 Export to other EU/EEA Member States

9.1 Export from the UK to other EU/EEA Member States of unlicensed medicinal products may take place if:

- they are manufactured in the UK by holders of a Manufacturer's "Specials" Licence;
- they are imported from within the EU/EEA by holders of a Wholesale Dealer's Licence (WDA(H)); or
- they are imported from outside the EU/EEA by holders of a Manufacturer's "Specials" Licence authorising import.

9.2 Holders of the above licences may export unlicensed medicinal products to other EU/EEA Member States, subject to the following conditions:

- national legislation in the receiving Member State, in accordance with Article 5(1) of Directive 2001/83/EC, as amended, permits importation and supply of unlicensed medicinal products;
- the UK exporter (i.e. the holder of a Manufacturer's "Specials" Licence or Wholesale Dealer's Licence) has assured himself that importation and supply of an unlicensed medicinal product is lawful in the Member State concerned before proceeding with the transaction;
- in the case of unlicensed medicinal products, imported into the UK for subsequent export to another Member State, the holder of a Manufacturer's "Specials" Licence or Wholesale Dealer's Licence is required to comply with the import notification requirements set out in Schedule 4 of the Human Medicines Regulations 2012 (see Section 5).

9.3 Regulation 167 of the Human Medicines Regulations 2012 applies only to supply to, or for use by, UK registered practitioners. There is no requirement that the individual patient for which the product is ordered is a UK national or resident. If the product is not supplied in the UK, but exported to another Member State for supply and use in that State, that supply is also governed by the relevant law in that State.

9.4 Unlicensed medicines for export to a non-EU/EEA Member State are not "specials". Such unlicensed medicines have to be manufactured by the holder of an ordinary Manufacturer's Licence, batch released and certified by a Qualified Person (QP).

10 European Court cases

Ludwigs-Apotheke München Internationale Apotheke v Juers Pharma Import-Export GmbH

10.1 The European Commission had referred to it by the German courts the case of Ludwigs-Apotheke München Internationale Apotheke verses Juers Pharma Import-Export GmbH in relation to the sending of price lists of medicinal products not approved in Germany. Juers Pharma the importer of unlicensed medicines sent a price list to

pharmacies. Whilst German legislation permitted importation of unlicensed medicines for individual use it prohibited advertising those products. The Court held that:

- the German provision allowing import of unlicensed medicines gave effect to Article 5(1) of Directive 2001/83;
- Title VIII (advertising) of Directive 2001/83 does not apply to the import of those unlicensed products;
- the German prohibition on the advertising of those products fell to be considered not in the light of Title VIII of Directive 2001/83 but the provisions of the EC Treaty concerning free movement of goods;
- a ban on advertising such as in this case which constitutes a measure having equivalent effect to a quantative restriction is justifiable for reasons connected with the protections of the health and life of humans in order to prevent the licensing system from being systematically undermined;
- but that the prohibition went beyond what was necessary because in the absence of information as to therapeutic effects, the lists at issue could not be capable of permitting pharmacists to recommend to their customers the importation of unlicensed products - and therefore an increase in such imports (which would undermine the licensing regime) was not plausible.

Ref: C-143/06 Ludwigs-Apotheke München Internationale Apotheke v Juers Pharma Import-Export GmbH

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:62006CJ0143:EN:HTML

European Commission v Republic of Poland

10.2 On 13/04/2010, the European Commission brought an action against the Republic of Poland regarding 'their failure to fulfil obligations concerning the authorisation of medicinal products for human use.' Specifically, the national law in Poland allowed the placing on the Polish market, without national authorisation, of medicinal products imported from outside Poland which were almost identical to those already authorised on that market, provided that the price of those foreign medicinal products was 'competitive' in relation to the price of the medicinal products which had obtained national authorisation.

10.3 The Commission argued that 'Article 5(1) of Directive 2001/83 makes it possible to derogate, for a particular medicinal product, from the requirement to have a national marketing authorisation where the medicinal product is supplied on account of a specific individual order and, not being on the national market, has to be imported, but it does not, in contrast, justify a derogation based on financial reasons.' As such, 'the European Commission considered this contrary to Article 6 of Directive 2001/83, in that it allowed certain medicinal products to be placed on the Polish market without prior marketing authorisation having been granted.'

10.4 The judgment of the Court was published on 29/03/2012 and found the following:

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

…

'It is apparent from the conditions as a whole set out in Article 5(1) of Directive 2001/83, read in the light of the fundamental objectives of that directive, and in particular the objective seeking to safeguard public health, that the derogation provided for in that provision can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market.'

…

'Financial considerations cannot, in themselves, lead to recognition of the existence of such special needs capable of justifying the application of the derogation provided for in Article 5(1) of that directive.'

10.5 The Court ruled in favour of the European Commission.

Ref: C-185/10 European Commission v Republic of Poland

http://curia.europa.eu/juris/document/document.jsf?text=&docid=121168&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=543667

11 Further information

11.1 Licence application forms are available from MHRA website www.mhra.gov.uk. Alternatively applicants can e-mail pcl@mhra.gsi.gov.uk or contact the PcL Enquiry Line on 020 3080 6844.

11.2 Copies of relevant statutory instruments are also available from the Legislation.gov.uk website: http://www.legislation.gov.uk/ or The Stationery Office, Publications Centre, PO Box 29, Norwich NR3 1GN, telephone 0870-600 5522.

11.3 Copies of the following MHRA Guidance Notes are available from MHRA's website:

MHRA Guidance Note 5:	Notes for applicants and holders of a Manufacturer's Licence
MHRA Guidance Note 6:	Notes for applicants and holders of a Wholesale Dealer's Licence
MHRA Guidance Note 8:	A guide to what is a medicinal product
MHRA Guidance Note 13:	A guidance note on Manufacturer's Licences authorising a non-orthodox practitioner to mix and assemble unlicensed medicinal products

MHRA Guidance Note 23:	The Blue Guide - Advertising and promotion of medicines in the UK
MHRA Guidance Note 25:	Best Practice Guidance on the labelling and packaging of medicines
MHRA Guidance Note 27:	Guidance notes for industry on the preparation of a Site Master File
MHRA Guidance Note 30:	Site Master File model: For Manufacturing "Specials" Licence holders or applicants for Manufacturing Authorisations relating to small-scale activities, including investigational medicinal products

12 Glossary of legislation

European legislation

Council Directive 2001/83/ EC on the Community code relating to medicinal products for human use as amended by 2004/27/EC and Directive 2004/24 EC and Directive 2002/98 EC

Legislation regulates the Licensing and Manufacture of and Wholesale dealing in Medicinal Products within the European Community.

Council Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products

This Directive lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture requires an authorisation.

UK legislation

The Human Medicines Regulations 2012 (SI 2012/1916)

Replaces nearly all UK medicines legislation – most of the Medicines Act 1968 and over 200 statutory instruments. The Regulations set out a comprehensive regime for the authorisation of medicinal products for human use; for the manufacture, import, distribution, sale and supply of those products; for their labelling and advertising; and for pharmacovigilance.

The Medicines (Products for Human Use) (Fees) Regulations 2013 (SI 2013/532)

These Regulations make provision for the fees payable under the Medicines Act 1971 in respect of marketing authorisations, licences and certificates relating to medicinal products for human use.

The Medicines for Human Use (Clinical Trials) Regulations (SI 2004/1031)

These Regulations implement Directive 2001/20/EC on the approximation of laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

The Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations (SI 2003/1680)

Regulates the importation and marketing of unlicensed medicinal products for human use in order to minimise the risk of the transmission of Transmissible Spongiform Encephalopathies via those products.

APPENDIX 1 - Extract from the Human Medicines Regulations 2012

Supply to fulfil special patient needs

167.—(1) 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.

(2) Condition A is that the medicinal product is supplied—

(a) to a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber; or

(b) for use under the supervision of a pharmacist in a registered pharmacy, a hospital or a health centre.

(3) Condition B is that no advertisement relating to the medicinal product is published by any person.

(4) Condition C is that—

(a) the manufacture and assembly of the medicinal product are carried out under such supervision; and

(b) such precautions are taken, as are adequate to ensure that the medicinal product meets the specification of the doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber who requires it.

(5) Condition D is that written records of the manufacture or assembly of the medicinal product in accordance with condition C are maintained and are available to the Licensing Authority or to the enforcement authority on request.

(6) Condition E is that if the medicinal product is manufactured or assembled in the United Kingdom or imported into the United Kingdom from a country other than an EEA State—

(a) it is manufactured, assembled or imported by the holder of a manufacturer's licence that relates specifically to the manufacture, assembly or importation of special medicinal products; or

(b) it is manufactured, assembled or imported as an investigational medicinal product by the holder of a manufacturing authorisation granted by the Licensing Authority for the purposes of regulation 36 of the Clinical Trials Regulations.

(7) Condition F is that if the product is imported from an EEA State—

(a) it is manufactured or assembled in that State by a person who is the holder of an authorisation in relation to its manufacture or assembly in accordance with the provisions of the 2001 Directive as implemented in that State; or

(b) it is manufactured or assembled as an investigational medicinal product in that State by the holder of an authorisation in relation to its manufacture or assembly in accordance with Article 13 of the Clinical Trials Directive as implemented in that State.

(8) Condition G is that if the product is distributed by way of wholesale dealing by a person ("P"), who has not, as the case may be, manufactured, assembled or imported the product in accordance with paragraph (6)(a) or (7)(a), P must be the holder of a wholesale dealer's licence in relation to the product in question.

(9) In this regulation "publish" has the meaning given in regulation 277(1) (interpretation: Part 14 advertising).

Record-keeping requirements

170.—(1) Where the sale or supply of a medicinal product relies on the exemptions under regulations 167, 168 or, subject to paragraph (4), 169, the person who sells or supplies the product must maintain for at least five years a record showing—

(a) the source from which and the date on which the person obtained the product;

(b) the person to whom and the date on which the sale or supply was made;

(c) the quantity of the sale or supply;

(d) the batch number of the batch of that product from which the sale or supply was made; and

(e) details of any suspected adverse reaction to the product so sold or supplied of which the person is aware or subsequently becomes aware.

(2) The person must make the records available for inspection by the Licensing Authority on request.

(3) The person must notify the Licensing Authority of any suspected adverse reaction to the medicinal product which is a serious adverse reaction.

(4) In the case of a medicinal product that is sold or supplied in reliance on the exemption in regulation 169—

(a) the reference in paragraph (1)(a) to “the product” means all the medicinal products that were mixed in the course of the manufacture of the product; and

(b) paragraph (1)(d) shall not apply.

APPENDIX 2 - Guidance on the hierarchy for the use of unlicensed medicines

This hierarchy is provided for guidance only and each case should be considered on its individual merit.

1. An unlicensed product should not be used where a product available and licensed within the UK could be used to meet the patient's special need.

2. Although MHRA does not recommend "off label" (outside of the licensed indications) use of products, if the UK licensed product can meet the clinical need, even "off-label", it should be used instead of an unlicensed product. Licensed products available in the UK have been assessed for quality safety and efficacy. If used "off-label" some of this assessment may not apply, but much will still be valid. This is better than the use of an un-assessed, unlicensed product. The fact that the intended use is outside of the licensed indications is therefore not a reason to use an unlicensed product. It should be understood that the prescriber's responsibility and potential liability are increased when prescribing off-label.

3. If the UK product cannot meet the special need, then another (imported) medicinal product should be considered, which is licensed in the country of origin.

4. If none of these options will suffice, then a completely unlicensed product may have to be used, for example, UK manufactured "specials", which are made in GMP inspected facilities, but which are otherwise un-assessed (GMP inspection of "specials" manufacturers is not product specific). There may also be other products available which are unlicensed in the country of origin.

5. The least acceptable products are those that are unlicensed in the country of origin, and which are not classed as medicines in the country of origin (but are in the UK). For example, the use of products from countries where they are classed as supplements, not pharmaceuticals, and may not be made to expected standards of pharmaceutical GMP. These should be avoided whenever possible.