THE SUPPLY OF UNLICENSED RELEVANT MEDICINAL PRODUCTS FOR INDIVIDUAL PATIENTS

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1 INTRODUCTION

1.1 The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for ensuring that medicines and medical devices work, are safe and of appropriate quality. The 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 Unless exempt, relevant medicinal products must have marketing authorisations or product licences before being placed on the market. In the UK an unlicensed relevant medicinal product may only be supplied in accordance with the provisions of Schedule 1 of **The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 [SI 1994/3144], (the MA Regs.)** Schedule 1 (see Appendix 1) exempts from the need for a marketing authorisation a relevant medicinal product which is supplied to fill a "special need" and in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients on his direct responsibility. In the interest of public health the exemption is narrowly drawn, because these products, unlike licensed products, may not have been assessed by the Licensing Authority against the criteria of safety, quality and efficacy.

1.3 The regulation of medicines on the UK market is undertaken by MHRA in accordance with the MA Regs, the Medicines Act 1968 ("the Act") and Regulations made under the Act.

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

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

- unlicensed herbal remedies supplied under Section 12 of the Act;
- homoeopathic medicines;
- investigational medicinal products;
- intermediate products;
- unlicensed medicinal products for export to third countries;
- products prepared in a pharmacy either in response to a prescription from a doctor or dentist for an individual patient or according to the prescriptions of a pharmacopoeia for a patient of that pharmacy;

- repackaged licensed products;
- reconstituted IV additives and CIVAS products.
- for compassionate use supply in accordance with Article 83 of Regulation (EC) 726/2004, for further advice: http://www.emea.europa.eu/pdfs/human/euleg/2717006enfin.pdf

1.6 This guidance also does not apply to licensed products:

- used outside the clinical indications of their licences, i.e. “off label” use.

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, telephone 01932-336911.

1.8 The Licensing Authority, for the purposes of the Act, legislation made under the Act and this guidance refers to the UK Ministers designated by the Act, acting either alone or jointly. The MHRA is the Government body set up to discharge the responsibilities of the Licensing Authority, under powers delegated by those Ministers.

2 PLACING ON THE MARKET

2.1 Relevant medicinal products are medicinal products for human use to which the 2001/83/EC Directive as amended applies. They include unlicensed medicinal products commonly referred to as “specials”.

2.2 An unlicensed medicinal product may only be placed on the market in order to meet the special needs of an individual 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 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.

2.3 As a rule, an unlicensed medicinal product which is a pharmaceutical equivalent of an available licensed medicinal product should not be placed on the market. A medicinal product should be regarded as a “pharmaceutical equivalent” if:

- it contains the same amount of the same active substance(s), or in the case of liquid dosage forms the same concentration; and
- it is in the same dosage form; and
- 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.

2.4 A licensed medicinal product obtainable from normal distribution channels in a reasonable time should be considered available for use. If an otherwise suitable licensed product becomes unavailable, it may be necessary for an unlicensed pharmaceutical 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 suitable licensed product.

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

- there is a bona fide unsolicited order;
- the product is formulated in accordance with the requirement of a doctor, dentist or supplementary prescriber registered in the UK;
- the product is for use by his individual patients on his direct personal responsibility;
- it is produced and supplied under specific conditions (see Sections 3 to11).

3 PERSONS AUTHORISED TO PROCURE “SPECIALS”

3.1 They are:

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

3.2 In all cases the supplier should take reasonable steps to establish that persons supplied satisfy the requirements of Schedule 1 to the MA Regs as amended, 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” declaring his professional status and stating that the product is required for the treatment of an individual patient. A retail pharmacist could state on the order that the product is for use solely in dispensing in accordance with prescriptions from doctors, dentists or a supplementary prescriber. 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. Hospital Trusts, Primary Care Trusts and independent hospitals should have clear policies on the use of unlicensed medicines, which reflect the differences in liability which may exist.

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 No. 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)[1] and the relevant provisions of **The Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005 [S.I. 2005/2789] (Manufacturing and Wholesale Dealing Regulations.)** 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 relevant pharmacopoeial monograph standards. 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 Manufacturing and Wholesale Dealing Regulations, an Inspector will also take account of product specifications, labelling, stability data and 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 the MHRA's guidance: Minimising the risk of Transmission of Transmissible Spongiform Encephalopathies via Unlicensed Medicinal Products for Human Use, available from the 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 section 10 of the Act.

[1] *Where possible GMP assured Active Pharmaceutical Ingredients should be used.*

Under these circumstances, the labelling of products prepared under section 10, and any documentation associated with them, should not make reference to the manufacturer's licence or number.

4.6 For guidance on labelling of unlicensed relevant medicinal products please refer to the pertinent paragraphs in the British Pharmacopoeia.

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 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 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 the Manufacturing and Wholesale Dealing Regulations. Specifically they require that where the licence relates to relevant medicinal products to which paragraph 1 of Schedule 1 to the MA Regs applies, the licence holder shall only import such products :-

(a) in response to an order which satisfies the requirements of paragraph 1 of Schedule1 to the MA Regs; and
(b) where the conditions set out in sub-paragraphs (2) to (9) below, are complied with.

(2) No later than 28 days prior to each importation of an exempt product, the licence holder shall give written notice to the Licensing Authority stating his intention to import that medicinal product and stating the following particulars:

(a) the name of the medicinal product, being the brand name or the common name, or the scientific name, and any name, if different, under which the medicinal product is to be sold or supplied in the United Kingdom;
(b) any trademark or the name of the manufacturer of the medicinal product
(c) in respect of each active constituent of the medicinal product, any international non-proprietary name or the British approved name or the monograph name or, where that constituent does not have an international non-proprietary name, a British approved name or a monograph name, the accepted scientific name or any other name descriptive of the true nature of that constituent;
(d) the quantity of medicinal product which is to be imported which shall not exceed 25 single administrations, or for 25 courses of treatment where the amount imported is sufficient for a maximum of three months’ treatment; and
(e) the name and address of the manufacturer or assembler of that medicinal product in the form in which it is to be imported and, if the person who will supply that medicinal product for importation is not the manufacturer or assembler, the name and address of such supplier.

(3) Subject to sub-paragraph (4), the licence holder shall not import the exempt imported product if, before the end of 28 days from the date on which the Licensing Authority sends or gives the licence holder an acknowledgement in writing by the Licensing Authority that they have received the notice referred to in sub-paragraph (2) above, the Licensing Authority have notified him in writing that the product should not be imported.

(4) The licence holder may import the exempt imported product referred to in the notice where he has been notified in writing by the Licensing Authority, before the end of the 28-day period referred to in subparagraph (3), that the exempt imported product may be imported.

(5) Where the licence holder sells or supplies exempt imported products, he shall, in addition to any other records which he is required by the provisions of his licence to make, make and maintain written records relating to—

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

(b) details of any adverse reaction to the product so sold or supplied of which he becomes aware.

(6) The licence holder shall import no more on any one occasion than such amount as is sufficient for 25 single administrations, or for 25 courses of treatment where the amount imported is sufficient for a maximum of three months' treatment, and on any such occasion shall not import more than the quantity notified to the Licensing Authority under sub-paragraph (2)(d).

(7) The licence holder shall inform the Licensing Authority forthwith of any matter coming to his attention which might reasonably cause the Licensing Authority to believe that the medicinal product can no longer be regarded either as a product which can safely be administered to human beings or as a product which is of satisfactory quality for such administration.

(8) The licence holder shall not issue any advertisement, catalogue, price list or circular relating to the exempt relevant medicinal product or make any representations in respect of that product.

(9) The licence holder shall cease importing or supplying an exempt imported product if he has received a notice in writing from the Licensing Authority directing that, as from a date specified in that notice, a particular product or class of products shall no longer be imported or supplied.

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 the MHRA's guidance: Minimising the risk of Transmission of Transmissible Spongiform Encephalopathies via Unlicensed Medicinal Products for Human Use, available from the 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 as amended defines wholesale distribution of medicinal products as all activities consisting of procuring, holding, supplying or exporting medicinal products within the EC or those countries covered by the EEA, apart from supplying medicinal products to the public. Where the licence relates to products to which the provisions of Directive 2001/83/EC as amended apply:-

- The holder of a Wholesale Dealer's Licence, must supply medicinal products only to persons who are themselves the holder of an authorisation granted by the competent authority of another Member State, other than the UK, authorising the supply of those products by way of wholesale distribution;

or

- any person who may lawfully supply medicinal products in circumstances corresponding to retail sale,

or

- any person who may lawful administer those products.

7 ADVERTISING

7.1 A “specials” manufacturer, importer or wholesaler may advertise the service he provides but particular “specials” must not be advertised. He may, however, respond to requests for information on specific products.

7.2 “Advertisement” includes catalogues, price lists, circular letters and internet notices.

8 HOLDING OF STOCKS BY DOCTORS, DENTISTS, PHARMACISTS

8.1 A doctor or dentist may prepare or procure a “special” for administration to one or more of his own patients. The amount of stock held per doctor or dentist is limited however, to a total of 5 litres of fluids or 2.5 kilograms of solids (such as tablets and capsules) of “specials” products.

8.2 A pharmacist in a hospital, health centre or a registered pharmacy may procure a stock of “specials” in order to meet an anticipated doctor’s ,dentist’s or supplementary prescriber’s prescription.

8.3 In either case where “specials” are procured they must be manufactured, imported or distributed by the holder of the appropriate licence.

9 OBLIGATIONS ON PERSONS WHO SELL OR SUPPLY

9.1 Any person selling or supplying “specials” must:

(a) keep the following records for 5 years:

- the source of the product;
- the person to whom and the date on which the product was sold or supplied;
- the quantity of each sale or supply;
- the batch number of the product;
- details of any adverse reactions to the product sold or supplied of which he is aware;

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

(c) report serious suspected adverse drug reactions (ADRs) to the 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 EMEA websites for more details). If it is not possible to electronically report, a paper company report form should be used and sent to: Unit Lead, Pharmacovigilance Information Unit, MHRA;

- doctors or pharmacists supplying the “special” should report using a Yellow Card form or an electronic Yellow Card (found at http://www.yellowcard.gov.uk), stating the manufacturer and indicating that the product is unlicensed.

9.2 These obligations are placed on any person selling or supplying “specials”, not only manufacturers, importers and distributors but also pharmacists, doctors, dentists and supplementary prescribers where appropriate.

10 EXPORT TO OTHER MEMBER STATES

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

- they are manufactured in the UK by holders of Manufacturer's "Specials" Licence (MS);
- they are imported from within the EU/EEA by holders of Wholesale Dealer's Licence (WL) or from outside the EU/EEA by holders of Manufacturer's "Specials" Licence for Import.

10.2 Holders of the above licences may export unlicensed relevant 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 of Directive 2001/83/EC, as amended, permits importation and supply of unlicensed relevant medicinal products;
- the UK exporter (i.e. the holder of an MS or WL) has assured himself that importation and supply of an unlicensed relevant medicinal product is lawful in the Member State concerned before proceeding with the transaction;
- in the case of unlicensed relevant medicinal products, imported into the UK for subsequent export to another Member State, the holder of a MS or WL is required to comply with the import notification requirements of Manufacturing and Wholesale Dealing Regulations (See Section 5).

10.3 The exemption, from the requirement to have a marketing authorisation, under Schedule 1 to the MA Regs applies to a product formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients. The exemption applies only to the supply of such a product to a doctor dentist or supplementary prescriber or for use in a registered pharmacy, a hospital or a health centre under the supervision of a pharmacist. Schedule 1 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, however, the product is not supplied in the UK, but exported to another Member State for supply and use in that State, that supply is governed by the relevant law in that State.

11 DISCLAIMER AND FURTHER INFORMATION

11.1 This MHRA Guidance Note should not be taken as a complete or definitive statement of the law. It is not intended as a substitute for legal or other professional advice. The MHRA accepts no liability for any loss or damage caused, arising directly or indirectly, in connection with reliance on the contents of this Guidance Note.

11.2 This Guidance note has been prepared in line with the Hampton Principles which state the following: regulators, and the regulatory system as a whole, should use comprehensive risk assessment to concentrate resources on the areas that need them most;

- regulators should be accountable for the efficiency and effectiveness of their activities, while remaining independent in the decisions they take;
- no inspection should take place without a reason;
- businesses should not have to give unnecessary information, nor give the same piece of information twice;
- the few businesses that persistently break regulations should be identified quickly;
- regulators should provide authoritative, accessible advice easily and cheaply; and
- regulators should recognise that a key element of their activity will be to allow, or even encourage, economic progress and only to intervene when there is a clear case for protection.

11.3 Licence application forms are available from the MHRA website www.mhra.gov.uk. Or e-mail pcl@mhra.gsi.gov.uk or contact the PcL Enquiry Line on 020 7084 2844 or write to PcL Enquiries, 17-1, MHRA, Market Towers, 1 Nine Elms Lane, London SW8 5NQ.

11.4 Copies of relevant statutory instruments are also available from the Office of Public Sector Information website: http://www.opsi.gov.uk/stat.htm or The Stationery Office, Publications Centre, PO Box 29, Norwich NR3 1GN, telephone 0870-600 5522.

11.5 Copies of MHRA Guidance Notes 5 and 6 are available from the MHRA website www.mhra.gov.uk or Information Centre, Medicines and Healthcare products Regulatory Agency, telephone 020 7084 2000.

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.

Primary legislation

Medicines Act 1968 as amended

This Act regulates in part the manufacture, distribution and importation of medicinal products.

Secondary legislation

The Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations (S.I. 2005 No: 2789)

Replaces, as respects medicinal products to which the relevant EU legislation applies ("relevant medicinal products"), the existing regulations which implement the Directive 2001/83/EC, as amended. Sets out the obligations with which holders of manufacturer's and wholesale dealer's licenses must comply in respect of those licences.

The Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Regulations (S.I. 1971 No: 974), as amended

These Regulations relates to applications for the grant of manufacturer's and wholesale dealer's licences other than licences of right. They prescribe the form and manner in which such applications are to be made, and specify the information that shall accompany each application.

Medicines (Manufacturer's Undertakings for Imported Products) Regulations (S.I. 1977 No:1038), as amended

These Regulations relate to prescribed Conditions for Manufacturer's undertaking imported products.

Medicines for Human Use (Marketing Authorisations etc) Regulations (S.I. 1994 No: 3144), as amended

Provide the functions for the Competent Authority of a member State under the relevant Community provisions Directive 2001/83/EC as amended by 2004/27/EC are, except as otherwise provided, to be performed in the UK by the Licensing Authority. They also provide that no medicinal product for human use which is subject to the relevant Community provisions may be placed on the market or distributed in the UK other than in accordance with a current marketing authorisation granted by the Licensing Authority or the European Commission.

The Medicines (Products for Human Use – Fees) Regulations (S.I. 1995 No:1116), as amended

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

The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004 No: 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 Sponigform Encephalopathies) (Safety) Regulations (S.I. 2003 No: 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.

Prescription Only Medicines (Human Use) Order (as amended) (S.I. 1997 No: 1830), as amended

This order specifies the descriptions and classes of prescription only medicines.

Guidance

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: Notes for manufacturer's licences authorising a non-orthodox practitioner to mix and assemble unlicensed medicinal products
MHRA Guidance Note 14: Supply of unlicensed relevant medicinal products for individual patients
MHRA Guidance Note 23: Advertising and promotion of medicines in the United Kingdom – The Blue Guide
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 28: Guidance notes for industry on the preparation of a Site Master File for an overseas site subject to inspection by the UK regulatory authority

APPENDIX 1
EXTRACT FROM SCHEDULE 1 OF THE MA REGS

1.

Regulation 3(1) shall not apply to a relevant medicinal product supplied in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor [, dentist or supplementary prescriber] and for use by his individual patients on his direct personal responsibility [, in order to fulfil the special needs of those patients], but such supply shall be subject to the conditions specified in paragraph 2.

2.

The conditions mentioned in paragraph 1 are that—

(a) the relevant medicinal product is supplied to a doctor [, dentist or supplementary prescriber] or for use in a registered pharmacy, a hospital or a health centre under the supervision of a pharmacist, in accordance with paragraph 1;

(b) no advertisement or representation relating to the relevant medicinal product is issued with a view to it being seen generally by the public in the United Kingdom and that no advertisement relating to that product, by means of any catalogue, price list or circular letter is issued by, at the request or with the consent of, the person selling that product by retail or by way of wholesale dealing or supplying it in circumstances corresponding to retail sale, or the person who manufactures it, and that the sale or supply is in response to a bona fide unsolicited order;

(c) if manufacture or assembly of the relevant medicinal product is carried out under the supervision of such staff and such precautions are taken as are adequate to ensure that the product is of the character required by and meets the specifications of the doctor[, dentist or supplementary prescriber] who requires it;

(d) written records as to the manufacture or assembly in accordance with sub-paragraph (c) are made and maintained and are available to the Licensing Authority or the enforcement authority on request by them or either of them;

(e) if the relevant medicinal product is manufactured or assembled in the United Kingdom, or imported into the United Kingdom from a third country, the product—

(i) is manufactured, assembled or imported by the holder of a manufacturer's licence which relates specifically to the manufacture, assembly or import of relevant medicinal products to which paragraph 1 applies; or

(ii) has been manufactured, assembled or imported as an investigational medicinal product by the holder of a manufacturing authorization granted by the Licensing Authority for the purposes of regulation 36 of the Medicines for Human Use (Clinical Trials) Regulations 2004; and]

(f) the relevant medicinal product is distributed by way of wholesale dealing by the holder of a wholesale dealer's licence.

3.

(1) Subject to the following sub-paragraphs, regulation 3(l) shall not apply to anything done—

(a) by a doctor or dentist which relates to a relevant medicinal product specially prepared by him, or to his order, for administration to one or more patients of his or, where that doctor or dentist is a member of a group of doctors or dentists working together to provide [primary medical services or general dental services], to one or more patients of any other doctor or dentist of that group, and consists of procuring the manufacture or assembly of a stock of the product with a view to administering the product to such patients; or

(b) in a registered pharmacy, a hospital or health centre and is done there by or under the supervision of a pharmacist, and consists of procuring the manufacture or assembly of a stock of relevant medicinal products with a view

(2) The exemption conferred by sub-paragraph (1) shall not apply to procuring the manufacture of relevant medicinal products unless those products are to be manufactured by the holder of a manufacturer's licence which relates specifically to the manufacture or assembly of relevant medicinal products to which paragraph 1 applies.

(3) The exemption conferred by sub-paragraph (1) shall not apply to anything done by a doctor or dentist in relation to a stock held by him of such relevant medicinal products in excess of a total of 5 litres of fluid and 2.5 kilograms of solids of all relevant medicinal products to which that sub-paragraph relates.

4.

(1) Regulation 3(1) shall not apply to the placing on the market by way of supplying of any relevant medicinal product to which this paragraph relates if the conditions of sub-paragraph (3) are satisfied.

(2) The relevant medicinal products to which this paragraph relates are relevant medicinal products which are for use by being administered to one or more human beings and which may be lawfully sold by retail or supplied in circumstances corresponding to retail sale, otherwise than in accordance with a prescription by a doctor or dentist.
(3) The conditions referred to in sub-paragraph (1) are—

(a) that the relevant medicinal product is sold or supplied to a person exclusively for use by him in the course of a business carried on by him for the purposes of administering it or causing it to be administered to one or more human beings otherwise than by selling it;

(b) that, if sold or supplied through the holder of a wholesale dealer's licence, the relevant medicinal product is sold or supplied to such a person, and for such use by him, as is described in head (a) above;

(c) that, where the manufacture or assembly of the relevant medicinal product is procured, it is procured by such a person, and for such use by him, as is described in head (a) above

(d) that no advertisement or representation relating to the relevant medicinal product is issued with a view to it being seen generally by the public in the United Kingdom and that no advertisement relating to that product, by means of any catalogue, price list or circular letter, is issued by, at the request or with the consent of, the person selling that product by retail or by way of wholesale dealing or supplying it in circumstances corresponding to retail sale, or the person who manufactures it, and that the sale or supply is in response to a bona fide unsolicited order;

(e) that the relevant medicinal product is prepared by or under the supervision of a pharmacist; and

(f) that the relevant medicinal product is manufactured by the holder of a manufacturer's licence which relates specifically to the manufacture of relevant medicinal products to which paragraph 1 applies.

5.

(1) Regulations 3(1) shall not apply to a radiopharmaceutical for human use—

(a) which is prepared at the time at which it is intended to be administered; and(b) which is prepared, in accordance with the manufacturer's instructions and by the person by whom it is to be administered, exclusively from a kit, generator or precursor (or from more than one of these) in respect of which a marketing authorization is in force; and

(c) the administration of which is not or will not be a contravention of regulation 2 of the Medicines (Administration of Radioactive Substances) Regulations 1978.

(2) In this paragraph—

"generator" means any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be removed by elution or by any other method and is to be used in a radiopharmaceutical;

"kit" means any preparation to be reconstituted or combined with radionuclides in a final radio pharmaceutical, usually prior to its administration.

"precursor" means a radionuclide produced for the radio-labelling of another substance prior to its administration, other than a radionuclide which is incorporated in or produced from a generator or is included in a radiopharmaceutical;

"radiopharmaceutical" means any relevant medicinal product which when ready for use contains one or more radionuclides included for a medicinal purpose.

[5A

Regulation 3(1) shall not apply to a medicinal product for which there is in force an authorization to place the product on the market granted by the Licensing Authority in accordance with Article 126a of the 2001 Directive.]

6.

Any person who sells or supplies a relevant medicinal product in accordance with any of paragraphs 1 to 4 shall maintain, and keep for a period of at least 5 years, a record showing—

(a) the source from which that person obtained that product;

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

(c) the quantity of each 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 he is aware.

7**.**

A person required to maintain the records mentioned in paragraph 6 shall—

(a) notify the Licensing Authority of any suspected adverse reaction such as is mentioned in head (e) of that paragraph which is a serious adverse reaction; and

(b) make available for inspection at all reasonable times by the Licensing Authority the records mentioned in that paragraph.

APPENDIX 2 CONTROL AND MONITORING OF STORAGE AND TRANSPORTATION TEMPERATURES

Legislation and good practices oblige pharmaceutical manufacturers and distributors to exercise control over the distribution chain to ensure that the quality of medicines is maintained. Critical in this regard is control of the environmental conditions under which medicines are stored and transported. The MHRA's recommendations concerning the control and monitoring of storage and transportation temperatures were published in The Pharmaceutical Journal in July 2001 (1). A summary of these is given below.

Introduction

1. EU requirements and guidelines on Good Distribution Practice (GDP) require distributors to 'ensure that storage conditions are observed at all times, including during transportation'. The requirements are applicable not only to medicines that need to be stored at low temperatures (known as cold chain products) but also to medicines that should be stored below 25º or 30º C (known as temperate chain products). In addition an increasing number of products require storage and transportation at sub-zero temperatures and the application of appropriate controls to these is equally important. What follows gives guidance on how compliance with relevant standards of good practice may be achieved.

Cold Storage

2. Many medicinal products require storage at controlled low temperature. Some of these such as vaccines, insulins, blood products and some products of biotechnology can be denatured by freezing and thus must be maintained within a narrow temperature range above freezing point.

3. The temperature in small refrigerators used to store medicines should be measured continuously and the maximum and minimum temperatures recorded daily. Sufficient space should be maintained to permit adequate air circulation. If the refrigerator is filled to capacity the effect on temperature distribution should be investigated. Refrigerators used for vaccines and other sensitive products should be capable of maintaining the temperature between 2°C and 8°C with the minimum of intervention. Temperature monitoring of these should be by electronic max/min thermometer, with an accuracy of + – 0.5°C, which should be readable from outside the unit. Refrigerators should not be sited in an environment where extremes of temperature (i.e. <10°C or >32°C) will affect their performance.

4. Large commercial refrigerators and walk-in cold rooms should be monitored with an electronic temperature-recording device that measures load temperature in one or more locations, depending on the size of the unit. Portable data-loggers that can be downloaded onto a computer may be used instead of a fixed device. Records should be checked daily. Internal air temperature distribution should be mapped on installation in the empty and full state and annually thereafter under conditions of normal use. Products should not be stored in areas shown by temperature mapping to present a risk (e.g. in the airflow from the refrigeration unit). Condensate from chillers should not be collected inside the unit.

5. Temperature alarms should be fitted to large and walk-in units and those smaller units used to store products at risk from freezing.

Controlled room temperature storage

6. The simplest monitoring would be with a max/min thermometer placed at a strategic location and read, recorded and reset at least weekly, more frequently during periods of exceptionally hot or cold weather. With the exception of very small stores, temperatures should be recorded at low and high levels. Continuous temperature recording is recommended for large warehouses. Self-contained storage areas within warehouses, (e.g. CD store, flammables store) should be included in temperature monitoring programmes.

7. All warehouses should be temperature mapped to determine the temperature distribution under extremes of external temperature. Mapping should be repeated every two to three years and after any significant modification to the premises, stock layout, or heating system. Medicines should not be stored in areas shown by temperature mapping or other consideration to be unsuitable, e.g. at high level in poorly insulated stores, or next to heaters.

Transportation

Cold-chain goods

8. The route and time of transportation, the local seasonal temperatures and the nature of the load should all be considered when arranging cold-chain distribution. For small volumes of cold-chain goods insulated containers may be used, in which case it is vital that products damaged by freezing are prevented from coming into direct contact with ice packs at subzero temperatures.

9. Larger volumes of cold-chain goods should be shipped in refrigerated transport, particularly if transit times may be prolonged. Temperatures within loads of products at risk

from freezing should be strictly controlled and monitored with recording probes or individual temperature monitoring devices, giving consideration to the temperature gradient within the load. The temperature records for each consignment should be reviewed and there should be a procedure for implementing corrective action in the case of adverse events.

10. Distributors should ensure that consignments of cold-chain goods are clearly labelled with the required storage/transport conditions Receivers should satisfy themselves that the goods have been transported under appropriate conditions and should place them in appropriate storage facilities as soon as possible after receipt.

Other goods

11. Consideration should be given to the possible extremes of temperature inside uninsulated, unventilated delivery vehicles and precautions should be taken to protect all products from heat challenge. This includes representatives' samples kept in car boots and goods distributed using postal services.

Systems Checks and Calibration

12. Any systems whose performance is critical to preserving the product should be tested and demonstrated to achieve what is intended. Measuring and recording devices that are used in critical areas (e.g. temperature monitoring of storage and transport facilities for coldchain goods at risk from freezing) should be calibrated at least annually against a traceable reference device. Records should include pre and post-calibration readings and details of any adjustments made or corrections to be applied. Alarms should be checked for correct functioning at the designated set temperatures.

Reference

(1) Taylor J, Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products. *The Pharmaceutical Journa*l, 28 July 2001, Volume 267, pages 128-131.