

NOTES FOR APPLICANTS AND HOLDERS OF A WHOLESALE DEALER'S LICENCE

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1 INTRODUCTION

1.1 The 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 Before a medicine can be marketed or sold in the UK, a number of licences are required. The product itself must have a licence called a 'marketing authorisation' (formerly a 'product licence') unless an exemption applies. In addition, the companies that are involved in all stages of the manufacture and distribution of the product need to have the relevant licence for the activity in question (manufacturer's and/or wholesale dealer's licences).

1.3 This Guidance has been published to assist applicants on how to obtain a Wholesale Dealer's Licence, to assist Wholesale Dealer's Licence holders and outline the key obligations for maintaining the licence.

1.4 The regulation of medicines on the UK market is undertaken by MHRA in accordance with **The Medicines Act 1968 (the Act) and Regulations made under the Act - The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 [SI 1994/3144], (the MA Regs.)**

1.5 UK legislation in respect of relevant medicinal products is in accordance with European Community Directives 2001/83/EC, as amended and 2003/94/EC. Relevant medicinal products are medicines for human use to which the 2001/83/EC Directive, as amended applies. The purpose of the Directive 2001/83/EC, as amended is to facilitate free movement of medicinal products by harmonising the rules governing the wholesale distribution of such products. The single market now extends additionally to members of the European Economic Area, i.e. Member States of the European Community plus Norway, Iceland and Liechtenstein. The Act and associated legislation have been amended in accordance with the Directive's provisions.¹

¹ This Guidance Note provides guidance on the law covering the wholesale distribution of medicinal products. The words "must" or "may" have been used to indicate legal requirements and the words "should" or "could" have been used to indicate guidance or recommendations.

1.6 The manufacture and distribution of veterinary 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.

1.7 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 Medicines and Healthcare products Regulatory Agency (MHRA) is the Government body set up to discharge the responsibilities of the Licensing Authority, under powers delegated by those Ministers.

2 WHOLESALE DEALING OR DISTRIBUTION

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

2.2 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.

2.3 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 a Member State authorising the supply of those products by way of wholesale distribution;
- or
- any person who may lawfully sell those products by retail or may lawfully supply them in circumstances corresponding to retail sale,
- or
- any person who may lawfully administer those products.

2.4 Veterinary medicinal products for use in animals are subject to different legislation. Advice on such products should be sought from the Veterinary Medicines Directorate of DEFRA, Woodham Lane, New Haw, Addlestone, Surrey, KT15 3LS, telephone 01932-336911.

3 PERSONS REQUIRING A WHOLESALE DEALER'S LICENCE

3.1 Persons who in the course of a business are engaged in:

- procurement, holding, or wholesale distribution of medicinal products for human use (including "specials")sourced in the UK or another EEA Member State;

require a wholesale dealer's licence (WL), unless exempt.

For advice on exemptions contact the MHRA Inspection and Standards Division Telephone: 0207 084 2442/2573 or check the MHRA website on www.mhra.gov.uk.

4 HOW TO OBTAIN A LICENCE

4.1 Application forms for a Wholesale Dealer's Licence (WL) are available from the MHRA website on www.mhra.gov.uk, the Licensing Office of the Inspection and Standards Division, MHRA, 17th Floor Market Towers, Nine Elms Lane, London, SW8 5NQ or via the Central Enquiry Point Telephone 020 7084 2000.

4.2 The Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Regulations 1971 as amended [SI 1971/974], require the following information to be provided to the Licensing Authority:-

- (a) name and address of applicant;
- (b) the period for which the licence is desired, if less than five years for products not covered by the 2001/83/EC Directive e.g. Products of Right;
- (c) the different classes of product to which the licence will relate, i.e. whether the products are Prescription Only Medicines (POM), Pharmacy medicines (P), General Sales List medicines (GSL) and herbal remedies, or other particular classes of product;
- (d) address of each site from which wholesale distribution (i.e. procurement, storage, sale, supply or export of medicinal products) takes place together with an indication of the general range of medicinal products to be stored at each;
- (e) a description of the facilities and equipment available at each site for storing the medicinal products and distributing products from or between the sites;
- (f) a description of the arrangements at each site for ensuring a satisfactory stock turnover.
- (g) the name, address, and qualifications of the Responsible Person (see section 6), details of an emergency plan for the recall of defective products and a description of arrangements for keeping records of all products received or dispatched;

4.3 The Licensing Authority will only issue a WL when it is satisfied, following an inspection of the site(s), that the information contained in the application is accurate and in compliance with the requirements of the legislation.

4.4 When appropriate, the Licensing Authority may refuse to grant a licence or may grant a licence otherwise than as applied for. In such cases the Licensing Authority will notify the applicant of its proposals. The notification will set out the reasons for its proposals and give

the applicant a period of not less than 28 days to respond. The applicant may either give notice to the Licensing Authority of his desire to be heard or make written representations to the Licensing Authority with respect to its proposals. Before determining the application the Licensing Authority shall give the applicant an opportunity of appearing before, and being heard by, a person appointed for the purpose by the Licensing Authority, or shall take those written representations into account, as the case may be.

5 WHOLESALE DEALER'S OBLIGATIONS

5.1 The holder of a wholesale dealer's licence must comply with certain obligations in relation to the wholesale distribution of relevant medicinal products. These obligations are set out in Regulations 8-11 of The Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005 [S.I. 2005/2789] (Manufacturing and Wholesale Dealing Regulations.) They require that the licence holder shall:

- (a) comply with the guidelines on good distribution practice²;
- (b) ensure, within the limits of his responsibility as a distributor of relevant medicinal products, the appropriate and continued supply of such relevant medicinal products to pharmacies and persons who may lawfully sell such products by retail or who may lawfully supply them in circumstances corresponding to retail sale;
- (c) provide and maintain such staff, premises, equipment and facilities for the handling, storage and distribution of the relevant medicinal products, in accordance with his licence as are necessary to maintain the quality of, and ensure proper distribution of the medicinal products (see Appendix 1);
- (d) inform the Licensing Authority of any proposed structural alteration to, or discontinued use of, premises to which the licence relates or premises which have been approved by the Licensing Authority;
- (e) inform the Licensing Authority of the name and address and degrees, diplomas or qualifications and experience of the person who will carry out the functions of the responsible person;
- (f) inform the Licensing Authority of any change to the responsible person.

5.2 The holder of a wholesale dealer's licence shall not sell or offer for sale or supply any relevant medicinal product unless:

- (a) there is a marketing authorisation for the time being in force in respect of that product; and
- (b) the sale or offer for sale is in accordance with the provisions of that authorisation.

5.3 The restrictions on the holder of a wholesale dealer's licence shall not apply to:

² *Guidelines on Good Distribution Practice (GDP) of medicinal products for human use (94/C63/03) and Rules and Guidance for Pharmaceutical Manufacturers and Distributors.*

- (a) the sale or offer for sale of any exempt relevant medicinal product; and
- (b) the export to an EEA State, or supply for the purposes of such export, of a relevant medicinal product which may be placed on the market in that State without a marketing authorisation by virtue of legislation adopted by that State under Article 5(2) of Directive 2001/83/EC, as amended.

5.4 The holder of a wholesale dealer's licence shall:

- (a) keep such documents relating to the sale of medicinal products to which his licence relates as will facilitate the withdrawal or recall from sale of relevant medicinal products in accordance with paragraph (b);
- (b) have in place an emergency plan which will ensure effective implementation of the recall from the market of any relevant medicinal products where such recall is:
 - (i) ordered by the Licensing Authority or by the competent authority of any other EEA State; or
 - (ii) carried out in co-operation with the manufacturer of, or the holder of the marketing authorisation for, the product in question;
- (c) keep such records, which may be in the form of purchase and sales invoices, or on a computer or in any other form, which give, as a minimum, where any relevant medicinal products are received or dispatched, the following information:
 - (i) the date of receipt or, as the case may be, dispatch,
 - (ii) the name of the relevant medicinal product,
 - (iii) the quantity received or, as the case may be, dispatched, and
 - (iv) the name and address of, as may be applicable in each case, the person from whom the products are received or to whom they are sold or supplied.

5.5 Where the holder of a wholesale dealer's licence imports from another EEA State any relevant medicinal product in respect of which he is neither the marketing authorisation holder in respect of that product; or acting on behalf of the marketing authorisation holder in importing that product, he shall notify the marketing authorisation holder and the Licensing Authority of his intention to import it. The obligation to inform Licensing Authority will be regarded as having been met if the distributor holds a UK parallel import licence covering that product.

5.6 The holder of a wholesale dealer's licence shall obtain supplies of relevant medicinal products only from:

- (a) a manufacturer's licence holder or wholesale dealer's licence holder in respect of such products; or
- (b) a person who holds an authorisation granted by another EEA State authorizing the manufacture of such products or their distribution by way of wholesale dealing.

5.7 The holder of a wholesale dealer's licence shall distribute relevant medicinal products by way of wholesale dealing only to:

- (a) a holder of a wholesale dealer's licence relating to those products;
- (b) a holder of an authorisation granted by the competent authority of another EEA State authorising the supply of those products by way of wholesale dealing;
- (c) any person who may lawfully sell those products by retail or who may lawfully supply them in circumstances corresponding to retail sale; or
- (d) any person who may lawfully administer those products.

5.8 Where any relevant medicinal product is supplied to any person who may lawfully sell those products by retail or who may lawfully supply them in circumstances corresponding to retail sale, the licence holder shall enclose with the product a document which makes it possible to ascertain:

- (a) the date on which the supply took place;
- (b) the name and pharmaceutical form of the product supplied;
- (c) the quantity of product supplied; and
- (d) the names and addresses of the person or persons from whom the products were supplied to the licence holder.

5.9 The licence holder shall:

- (a) keep a record of the information supplied where any relevant medicinal product is supplied to any person who may lawfully sell those products by retail or who may lawfully supply them in circumstances corresponding to retail sale for a minimum period of five years after the date on which it is supplied; and
- (b) ensure, during that period, that that record is available to the Licensing Authority for inspection.

5.10 Where a wholesale dealer's licence relates to relevant medicinal products, the wholesale dealer's licence holder shall at all times have at his disposal the services of a responsible person who, in the opinion of the Licensing Authority:

(a) has knowledge of the activities to be carried out and of the procedures to be performed under the licence which is adequate for performing the functions of responsible person; and

(b) has experience in those procedures and activities which is adequate for those purposes.

5.11 The functions of the responsible person shall be to ensure, in relation to relevant medicinal products, that the conditions under which the licence has been granted have been, and are being, complied with and the quality of relevant medicinal products which are being handled by the wholesale dealer's licence holder are being maintained in accordance with the requirements of the marketing authorisations applicable to those products.

5.12 The standard provisions for wholesale dealer's licences, that is, those provisions which may be included in all licenses unless the licence specifically provides otherwise, insofar as those licences relate to relevant medicinal products, shall be those provisions set out in Schedule 4 of The Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005 [S.I. 2005/2789].

5.13 The licence holder shall not use any premises for the purpose of the handling, storage or distribution of relevant medicinal products other than those specified in his licence or notified to the Licensing Authority by him and approved by the Licensing Authority.

5.14 The licence holder shall provide such information as may be requested by the Licensing Authority concerning the type and quantity of any relevant medicinal products which he handles, stores or distributes.

5.15 The licence holder, for the purpose of enabling the Licensing Authority to ascertain whether there are any grounds:

(a) for suspending, revoking or varying any licence granted under Part II of the Act; or

(b) suspending or terminating any licence in accordance with the provisions of Part II of the Act, shall permit, and provide all necessary facilities to enable, any person duly authorised in writing by the Licensing Authority, on production if required of his credentials, to carry out such inspection or to take such samples or copies, in relation to things belonging to, or any business carried on by, the holder of the licence, as such person would have the right to carry out or take under the Act for the purpose of verifying any statement contained in an application for a licence.

5.16 Where and insofar as the licence relates to relevant medicinal products to which paragraph 1 of Schedule 1 to the MA Regs apply which do not have a UK or EMEA (European Medicines Agency) authorisation and are commonly known as “specials” (refer to Guidance Note 14), the licence holder shall only import such products from another EEA State:

(i) in response to an order which satisfies the requirements of paragraph 1 of Schedule 1 to the MA Regs; and

(ii) where the following conditions are complied with:

(1) No later than 28 days prior to each importation of an exempt imported 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 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 the quantity specified in sub-paragraph (5); and

(f) 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.

(2) Subject to sub-paragraph (3), 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 (1) above, the Licensing Authority have notified him in writing that the product should not be imported.

(3) 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 (2), that the exempt imported product may be imported.

(4) 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:

- (i) the batch number of the batch of the product from which the sale or supply was made; and
- (ii) details of any adverse reaction to the product so sold or supplied of which he becomes aware.

(5) 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 subparagraph (1)(d).

(6) 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.

(7) 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.

(8) 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.

5.17 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 handles, stores or distributes is not false or misleading in a material particular.

6 RESPONSIBLE PERSON

6.1 Directive 2001/83/EC as amended requires that all licensed wholesale dealers should have at their disposal a Responsible Person (RP). In the UK this requirement is set out at Regulation 10 of the Manufacturing and Wholesale Dealing Regulations. The RP is responsible for safeguarding product users against potential hazards arising from poor distribution practices - as a result, for example, of supplying suspect products, poor storage or failure to establish the bona fides of suppliers and purchasers.

6.2 The RP must ensure that a quality management system is implemented and maintained. He/she must ensure that the conditions of the wholesale dealer's licence (WL) are being complied with and that the guidelines on Good Distribution Practice (GDP) are met. If the RP is not adequately carrying out his duties, the Licensing Authority may consider, the suspension of the licence, withdrawal of acceptance of the RP on that licence, and review his acceptability to be named on any other licence.

6.3 The RP does not have to be an employee of the licence holder but he must be at his continuous disposal. Where the RP is not an employee there should be a written contract that specifies his responsibilities, duties, authority and so on.

6.4 There is no statutory requirement for the RP to be a pharmacist, although this is desirable. However, he should have access to pharmaceutical knowledge and advice when it is required and have personal knowledge of:

- (a) The relevant provisions of the Act, the Manufacturing and Wholesale Dealing Regulations and the MA Regs.
- (b) Articles 76-85 of Directive 2001/83/EC as amended on the Community Code relating to medicinal products for human use, as amended.
- (c) European Commission Guidelines on good distribution practice of medicinal products for human use (94/C 63/03).
- (d) The conditions attached to the WL for which he is nominated.
- (e) The products traded under the licence and the conditions necessary for their safe storage and distribution.
- (f) The categories of persons to whom products may be distributed.
- (g) The Quality System and Standard Operating Procedures employed by the WL holder.

6.5 Where the RP is not a pharmacist or eligible to act as a Qualified Person (QP) (as defined in Directive 2001/83/EC as amended) he should have at least one year's practical experience in both or either of the following areas:

- (a) Handling, storage and distribution of medicinal products.

(b) Selling, supplying or procuring medicinal products.

6.6 In addition, the RP should have at least one year's managerial experience in controlling and directing the activity of the wholesale distribution of medicinal products on a scale, and of a kind, appropriate to the licence for which nominated.

6.7 It is for the Licensing Authority to determine if a particular RP has the appropriate knowledge and experience for the scale and nature of the wholesale distribution operation to which he is nominated.

6.8 To carry out his responsibilities the RP should:

(a) Have a clear reporting line to either the licence holder or, where the licence holder is a company, to the Managing Director.

(b) Have access to all areas, sites, stores and records which relate to the licensable activities being carried out.

(c) Regularly review and monitor all such areas, sites, etc. or have delegated arrangements whereby he receives written reports that such actions have been carried out on his behalf. For example, where the licence covers a number of sites the RP may have nominated deputies. However, the RP should assure himself and the Licensing Authority that the necessary controls and checks are in place. The RP remains responsible and he should personally carry out the delegated functions at least once a year.

(d) Focus on the management of licensable activities, the accuracy and quality of records, compliance with established standard operating procedures, the quality of handling and storage equipment and facilities, and the standards achieved.

(e) Keep appropriate records relating to the discharge of his responsibilities.

6.9 The licence holder should ensure that there is a written Standard Operating Procedure (SOP) for receiving advice and comment from the RP and recording the consequent action taken.

6.10 Should it prove impossible to resolve a disagreement between the licence holder and the RP with regard to the statutory duties and responsibilities of the responsible person under the licence, the Licensing Authority should be approached for advice. Whilst a joint referral is clearly to be preferred, either party may approach the Licensing Authority for advice independently. If a RP finds that he is in difficulty over his statutory responsibilities and the activities being carried out under the licence he should, in strict confidence, consult the Licensing Authority.

7 INSPECTION

7.1 The GDP Inspectorate carries out regular and repeated inspections of wholesale distribution sites. Inspection enables the Licensing Authority to confirm that licence holders are complying with the conditions of their licence, with the provisions of the Act and with the requirements of Good Distribution Practice (GDP).

7.2 Amongst other things, GDP Inspectors are empowered to:

- (a) inspect the premises, organised arrangements and procedures used in the storage and distribution of medicinal products;
- (b) interview key personnel named on licences;
- (c) take samples;
- (d) require production and examine any documentation or records relating to the manufacture, assembly, storage and distribution of medicinal products in accordance with Part 8 of the Act.

It is a requirement of both EC and UK national legislation that licence holders shall make their premises available for inspections by the Licensing Authority at any reasonable time.

7.3 A fee is charged for these inspections. See Section 10 Fees.

7.4 Following an inspection, the GDP Inspector prepares a report of his findings. A letter is sent to the licence applicant or holder noting any deficiencies found and asking for proposals to remedy them. In the most serious cases the report is referred to the Licensing Authority for considering more formal action which can include the refusal i.e. refusal before a licence is granted, making a variation to an existing licence, suspension or revocation of a licence, or suspension or revocation of part of a licence or take action relating to the activities or omissions of the RP.

8 COUNTERFEIT AND DIVERTED MEDICINES

Counterfeit Medicines

8.1 The supply of counterfeit medicines is a growing problem worldwide and one which the MHRA is taking very seriously. Counterfeit medicines represent an increasing threat to the legitimate UK supply chain and to patient safety. They are frequently defective and deliberately mislabelled with respect to identity, composition, and source. Counterfeiting can apply to both innovator and generic products, prescription and self-medication products, as well as to traditional herbal remedies. Counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients, and may even contain harmful or poisonous substances.

8.2 The supply and distribution of medicines is tightly controlled within the European Community. All licensed wholesalers must comply with the Community's agreed standards of GDP and there exist strict licensing and regulatory requirements in UK domestic legislation to safeguard patients against potential hazards arising from poor distribution practices – for example, purchasing suspect or counterfeit products, failing to establish the “bona fides” of suppliers and purchasers and inadequate record keeping.

8.3 Of principal importance to manufacturers and wholesale dealers is paragraph 31 of the EU Guide to GDP, which states:

"Counterfeit medicinal products found in the distribution network should be kept apart from other medicinal products to avoid any confusion. They should be clearly labelled as not for sale and competent authorities and the holder of marketing authorisation of the original product should be informed immediately"

8.4 Manufacturers and wholesale dealers should inform the Licensing Authority of any defect that could result in a recall or abnormal restriction on the supply of a product. They must also have effective recall procedures in place.

8.5 Wholesale dealers in particular should maintain a high level of vigilance against the procurement or supply of potentially counterfeit product. Such product may be offered for sale below the established market price so rigorous checks should be made on the bona fides of the supplier and the origin of the product.

8.6 The Licensing Authority will take regulatory action where breaches of legislation are identified. This may take the form of adverse licensing action e.g. compulsorily varying an

existing licence, suspension or revocation of a licence and/or the instigation of criminal proceedings.

Diverted Medicines

8.7 Diversion is the term used for the fraudulent activity where medicines destined for a non EU market re-enter the EU and are placed back on to the European market at a higher price.

8.8 The diversion of medicines involves medicinal products being offered at preferential prices for export to specific markets (normally developing countries) outside the EU. Diversion occurs when unscrupulous traders, on receipt of the medicines, re-export the pharmaceutical products back to the EU - meaning that patients for whom these preferentially-priced medicines were intended, are denied access to them. Such products appearing on the EU market are then known as “diverted” from their intended market. This represents not only a corrupt diversion for profit but such activity also poses the risk of inappropriate or unlicensed use and the quality of the diverted product may also be seriously compromised.

8.9 As with counterfeit products, wholesale dealers in particular should maintain a high level of vigilance against the procurement or supply of potentially diverted product. Such product may be offered for sale below the established market value, so appropriate checks should be made on the bona fides of the supplier and the origin of the product.

8.10 The Licensing Authority will take regulatory action where breaches of legislation are identified. This may take the form of adverse licensing action e.g. compulsorily varying an existing licence, suspension or revocation of a licence and/or the instigation of criminal proceedings.

9 POWERS TO VARY, SUSPEND OR REVOKE WHOLESALE DEALER'S LICENCES

9.1 The Licensing Authority may revoke, vary or suspend a licence when a condition of that licence is no longer being met. The Licensing Authority will serve on the licence holder a notice stating its proposals with reasons. The licence holder will be given a period of not less than 28 days to respond. The licence holder may give notice to the Licensing Authority of his desire to be heard, or make written representations to the Licensing Authority with respect to its proposals. Before determining the matter the Licensing Authority will afford him an opportunity of appearing before, and being heard by, a person appointed for the purpose by the Licensing Authority, or will take those written representations into account, as the case may be.

9.2 Where it appears to the Licensing Authority that public safety is at risk it may also suspend the licence with immediate effect for a period of up to three months. This suspension may be renewed for further periods of up to three months if the Licensing Authority considers this necessary.

9.3 Licence provisions may be varied on the application of the licence holder.

9.4 A licence holder or applicant may at any time within the period of three months from the date on which notice of the decision is served on him make an application to the High Court to judicially review the validity of the Licensing Authority's decision.

10 FEES

10.1 The Medicines Act 1971 introduced provisions for the payment of fees for licences, certificates and inspections. The current fees legislation for human medicinal products is contained in The Medicines (Products for Human Use - Fees) Regulations SI 1995/1116 as amended.

10.2 Fees are currently payable for the following:

- (a) licence applications;
- (b) licence variations;
- (c) inspections.

10.3 An annual service charge is also payable during the currency of a licence.

10.4 A schedule of the current fees is available on request from the website info@mhra.gsi.gov.uk or Information Centre, 10-2 Market Towers, 1 Nine Elms Lane, London SW8 5NQ, Telephone: 020 7084 2000.

10.5 When the Agency plans to make changes to the amount or frequency of fees, licence holders are consulted and given the opportunity to comment on the MHRA's proposals. Details of consultation letters (known as MLXs) are published in *MAIL*(1) and the MHRA website www.mhra.gov.uk.

11 FURTHER INFORMATION

11.1 Extracts from the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 as amended [SI 1971/972]; Council Directive 2001/83/EC as amended, and guidelines on good distribution practice of medicinal products for human use (94/C63/03) and notes on duties of the RP and QP are published in *Rules and Guidance for Pharmaceutical Manufacturers and Distributors* (“The Orange Guide”) available from TSO (The Stationery Office) (www.tso.co.uk/bookshop). Please note the “Orange Guide” does not reflect recent legal changes and is under revision.

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

11.3 From the 30 October 2005, The Veterinary Medicines Regulations 2005 [SI 2005/2745] provide that the Medicines Act 1968 will no longer apply to veterinary medicinal products. From this date manufacturers and distributors of veterinary medicines must comply with the provisions of the Veterinary Medicines Regulations 2005 in respect of the manufacture of and wholesale dealing in veterinary medicinal products. If you have any specific issues or points about the Veterinary Medicines Regulations 2005, and specifically further advice on the provisions relating to the manufacture and distribution of veterinary medicines please contact the Veterinary Medicines Directorate at DEFRA.

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 Spongiform 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 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 25° or 30° 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 sub-zero 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 cold-chain 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 Journal*, 28 July 2001, Volume 267, pages 128-131.