STATUTORY INSTRUMENTS

2010 No. 1882

MEDICINES

The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010

Made - - - -	*21st July 2010*
Laid before Parliament	*26th July 2010*
Coming into force - -	*19th August 2010*

The Secretary of State and the Minister for Health, Social Services and Public Safety make the following Regulations acting jointly, in exercise of the powers conferred on them by sections 8(2D)(**1**), 8(3E)(**2**),18(1), 47(1) and 129(1) and (5) of the Medicines Act 1968(**3**), or, in the case of the Minister, the powers conferred by those provisions and now vested in him(**4**).

The Secretary of State is a Minister designated(**5**) for the purposes of section 2(2) of the European Communities Act 1972(**6**) in relation to medicinal products, in exercise of the powers conferred on him by that section.

In accordance with section 129(6) of the Medicines Act 1968, they have consulted such organisations as appear to them to be representative of interests likely to be substantially affected by these Regulations.

Citation, commencement and interpretation

1.—(1) These Regulations may be cited as the Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010 and shall come into force on 19th August 2010.

(2) In these Regulations—

"the Act" means the Medicines Act 1968(**7**);

(**1**) Section 8(2D) was inserted by S.I. 2005/2789. *See* section 132(1) for the definition of "prescribed".
(**2**) Section 8(3E) was inserted by S.I. 2005/2789.
(**3**) 1968 c.67. The expression "the Ministers", which is relevant to the powers being exercised in the making of these Regulations, is defined in section 1 of the Medicines Act 1968 as amended by paragraph 1(1) of the Schedule to S.I. 1999/3142 and paragraph 2 of Part 1 of Schedule 8 to S.I. 2006/2407.
(**4**) By virtue of section 95(5) of, and paragraph 10 of Schedule 12 to, the Northern Ireland Act 1998 (c.47); the Department for which the Minister is responsible was renamed by virtue of Article 3(6) of S.I. 1999/283 (N.I.1.).
(**5**) S.I. 1972/1811.
(**6**) 1972 c.68. Section 2(2) was amended by the Legislative and Regulatory Reform Act 2006, section 27(1)(a).
(**7**) 1968 c.67.

"advanced therapy medicinal product" has the meaning that expression bears in paragraph 1(a) of Article 2 of Regulation (EC) No. 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products(**8**);

"the Directive" means Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use(**9**);

"exempt advanced therapy medicinal product" means an advanced therapy medicinal product of the kind described in Article 3.7 of the Directive;

"the guidelines on good distribution practice" means the Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03) published by the European Commission pursuant to Article 84 of the Directive; and

"the principles and guidelines of good manufacturing practice" means the principles and guidelines of good manufacturing practice set out in Commission Directive 2003/94/EC(**10**) and the guidelines drawn up pursuant to Article 5 of Regulation (EC) 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products.

Disapplication of section 7 of the Medicines Act 1968 to exempt advanced therapy medicinal products

2. Section 7 of the Act(**11**) (dealing with medicinal products and product licences) shall not apply in relation to an exempt advanced therapy medicinal product.

Licence conditions for exempt advanced therapy medicinal products

3.—(1) The requirements in Schedule 1 have effect as provisions of any manufacturer's licence insofar as such a licence relates to an exempt advanced therapy medicinal product.

(2) The standard provisions, for the purposes of Part II of the Act, for manufacturer's licences insofar as those licences relate to exempt advanced therapy medicinal products are set out in Schedule 2.

(3) The requirements in Schedule 3 have effect as provisions of any wholesale dealer's licence insofar as such a licence relates to an exempt advanced therapy medicinal product.

(4) The standard provisions, for the purposes of Part II of the Act, for wholesale dealer's licences insofar as those licences relate to exempt advanced therapy medicinal products are set out in Schedule 4.

Traceability

4.—(1) A person who treats a patient with an advanced therapy medicinal product commits an offence if there is no system in place for patient and product traceability in relation to such treatment containing sufficient detail to enable the linking of the product to the patient who received it and vice versa.

(**8**) OJNo. L 324, 10.12.07, p.121.
(**9**) OJ No. L 311, 28.11.2001, p.67; relevant amending instruments are Directive 2002/98/EC of the European Parliament and of the Council (OJ No. L 33, 8.2.2003, p.30), Commission Directive 2003/63/EC (OJ No. L 159, 27.6.2003, p.46), Directive 2004/24/EC of the European Parliament and of the Council (OJ No. L 136, 30.4.2004, p.85), Directive 2004/27/EC of the European Parliament and of the Council (OJ No. L 136, 30.4.2004, p.34), Regulation (EC) No. 1901/2006 of the European Parliament and of the Council (OJ No. L 378, 27.12.2006, p.1), Regulation (EC) No. 1394/2007 of the European Parliament and of the Council (OJ No. L 324, 10.12.2007, p.121), Directive 2008/29/EC of the European Parliament and of the Council (OJ No. L 81, 20.3.2008, p.51), Directive 2009/53/EC of the European Parliament and of the Council (OJ No. L 168, 30.6.2009, p.33) and Commission Directive 2009/120/EC (OJ No. L 242, 15.9.2009, p.3).
(**10**) OJ No. L 262, 14.10.2003.
(**11**) Section 7 was amended by S.I.1977/1050, 1983/1724, 1992/604, 1994/276, 2004/1031, 2005/50, 2005/2753 and 2006/2407.

(2) A person who treats a patient with an advanced therapy medicinal product commits an offence if the treatment involves a product which contains human cells or tissues, the traceability system referred to in paragraph (1) is not complementary to, and compatible with, the requirements laid down in—

(a) Articles 8 and 14 of Directive 2004/23/EC(**12**) as regards human cells and tissues other than blood cells, and

(b) Articles 14 and 24 of Directive 2002/98/EC(**13**) as regards blood cells.

(3) It is a defence to an offence under paragraph (1) or, as the case may be, paragraph (2) if the person who treats a patient was assured in writing before the treatment was given that a system of traceability as described in paragraph (1) or, as the case may be, paragraph (2) was in place in relation to the treatment given by that person.

(4) It is an offence for a person to give an assurance in writing to a person ("P") who treats a patient with an advanced therapy medicinal product that a system of traceability as described in paragraph (1) or paragraph (2) is in place in relation to treatment with an advanced therapy medicinal product given by P if no such system is in place.

(5) Any person guilty of an offence under paragraph (1), (2) or (4) shall be liable—

(a) on summary conviction, to a fine not exceeding the statutory maximum; or

(b) on conviction on indictment, to a fine or to imprisonment for a term not exceeding two years or to both.

Traceability in the event of bankruptcy or liquidation of holder of manufacturer's licence for exempt ATMP

5. Paragraphs 13C(**14**), 14 and 17(**15**) of Schedule 3 (offences, penalties etc.) to the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994(**16**) apply to the holder of a manufacturer's licence in respect of an exempt advanced therapy medicinal product as though in paragraph 13C—

(a) the reference to the holder of a marketing authorisation were a reference to the holder of a manufacturer's licence relating to an exempt advanced therapy medicinal product; and

(b) the reference to the European Medicines Agency established by Regulation (EC) No. 726/2004(**17**) were a reference to the licensing authority.

Amendment of the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971

6. In the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971—

(a) after regulation 1A(**18**) (veterinary medicinal products), insert—

(**12**) OJ No. L 102, 7.4.2004, p.48.
(**13**) OJ No. L 33, 8.2.2003, p.30.
(**14**) Paragraph 13C is inserted by paragraph 3(4) of Schedule 5 to these Regulations.
(**15**) Paragraph 17 was inserted by S.I. 2005/1710 and amended by S.I. 2008/3097.
(**16**) S.I. 1994/3144.
(**17**) OJ No. L 136, 30.4.2004, p.1.
(**18**) S.I. 1971/972. Regulation 1A was inserted by S.I. 2005/2745 and revoked by S.I. 2005/2789 in relation to manufacturers' licences and wholesale dealers' licences insofar as such licences relate to relevant medicinal products as defined in S.I. 2005/2789.

"**Advanced therapy medicinal products which are not relevant medicinal products**

1B.—(1) These Regulations do not apply in relation to exempt advanced therapy medicinal products.

(2) In this regulation—

(a) "advanced therapy medicinal product" has the meaning that expression bears in paragraph 1(a) of Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products; and

(b) "an exempt advanced therapy medicinal product" means a product of the kind described in Article 3.7 of the 2001 Directive."; and

(b) in regulation 2(**19**) (interpretation) for the definition of "the 2001 Directive" substitute—

""the 2001 Directive" means Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicines for human use, as amended by—

(a) Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components,

(b) Commission Directive 2003/63/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use,

(c) Directive 2004/24/EC of the European Parliament and of the Council amending, as regards traditional herbal medicinal products Directive 2001/83/EC on the Community code relating to medicinal products for human use,

(d) Directive 2004/27/EC of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code relating to medicinal products for human use,

(e) Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006,

(f) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007,

(g) Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008,

(h) Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009, and

(i) Commission Directive 2009/120/EC of 14 September 2009;".

Amendment of the Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Regulations 1971

7.—(1) The Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Regulations 1971(**20**) are amended in accordance with the following paragraphs.

(2) In regulation 2(1) (interpretation)—

(a) after the definition of "the Act", insert—

(**19**) Relevant amending instruments are S.I. 2002/236, 2003/2321 and 2005/2789.
(**20**) S.I. 1971/974; relevant amending instruments are S.I. 1977/1052, 1978/1140, 1983/1725, 1993/832, 2002/236 and 2005/2789.

""advanced therapy medicinal product" has the meaning that expression bears in paragraph 1(a) of Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products;";

(b) for the definition of "the 2001 Directive" substitute—

""the 2001 Directive" means Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicines for human use, as amended by—

(a) Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components,

(b) Commission Directive 2003/63/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use,

(c) Directive 2004/24/EC of the European Parliament and of the Council amending, as regards traditional herbal medicinal products Directive 2001/83/EC on the Community code relating to medicinal products for human use,

(d) Directive 2004/27/EC of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code relating to medicinal products for human use,

(e) Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006,

(f) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007,

(g) Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008,

(h) Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009, and

(i) Commission Directive 2009/120/EC of 14 September 2009;";

(c) after the definition of "the 2001 Directive", insert the following definition—

""exempt advanced therapy medicinal product" means a product of the kind described in Article 3.7 of the 2001 Directive;".

(3) In Schedule 1 (particulars required on an application for the grant of a manufacturer's licence), add after paragraph 10—

"**11.** Where the application relates to an exempt advanced therapy medicinal product, an outline of the arrangements for maintaining records to allow product traceability containing sufficient detail to enable the linking of a product to the patient who received it and vice versa.".

Amendment of the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994

8. The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994(**21**) are amended in accordance with Schedule 5.

(**21**) S.I. 1994/3144.

Amendment of the Medicines for Human Use (Clinical Trials) Regulations 2004

9.—(1) The Medicines for Human Use (Clinical Trials) Regulations 2004(**22**) are amended in accordance with the following paragraphs.

(2) In regulation 15(10) (ethics committee opinion)—

(a) in the definition of "the specified period", in sub-paragraph (a), after "genetically modified organism" insert "or a tissue engineered product"; and

(b) for the definition of "specialist group or committee" substitute—

> ""specialist group or committee" means a group or committee whose functions include the provision of advice on ethical or scientific issues in relation to—
>
> (a) tissue engineered products;
>
> (b) in the case of medicinal products for gene therapy or somatic cell therapy, the use of such therapies in the treatment of humans; or
>
> (c) in the case of medicinal products containing genetically modified organisms, the administration of such products to humans.".

(3) In regulation 19 (authorisation procedure for clinical trials involving medicinal products for gene therapy etc.), for paragraph (1) substitute—

> "(1) This regulation applies to clinical trials involving—
>
> (a) medicinal products for gene therapy and somatic cell therapy, including xenogenic cell therapy;
>
> (b) medicinal products containing genetically modified organisms; or
>
> (c) tissue engineered products.".

(4) In paragraph 8(4) of Schedule 2 (co-opting members to the Gene Therapy Advisory Committee), for "Paragraph (3)" substitute "Sub-paragraph (3)".

Amendment of the Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005

10. In the Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005(**23**)—

(a) in regulation 1(2) (citation, commencement and interpretation), for the definition of "relevant medicinal product" substitute—

> ""relevant medicinal product" means a medicinal product for human use to which the provisions of the Directive apply other than an advanced therapy medicinal product within the meaning that expression bears in paragraph 1(a) of Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products;"; and

(b) in—

(i) paragraph 7(8) of Schedule 2 (standard provisions which may be incorporated in a manufacturer's licence relating to the import of relevant medicinal products from a third country); and

(ii) paragraph 3(8) of Schedule 4 (standard provisions which may be incorporated in a wholesale dealer's licence),

delete ", price list".

(**22**) S.I. 2004/1031; relevant amending instruments are S.I. 2005/2754, 2006/1928 and 2008/941.
(**23**) S.I. 2005/2789.

Signed by authority of the Secretary of State for Health.

Earl Howe
Parliamentary Under-Secretary of State,
21st July 2010 Department of Health
Andrew McCormick
Permanent Secretary, Department of Health,
21st July 2010 Social Services and Public Safety

SCHEDULE 1

Regulation 3(1)

Requirement that holders of manufacturer's licences comply with certain obligations in relation to the manufacture and assembly of exempt advanced therapy medicinal products

A holder of a manufacturer's licence must—

(a) comply with the principles and guidelines of good manufacturing practice;

(b) maintain such staff, premises, equipment and facilities—

(i) as are necessary for such stages of the manufacture and assembly of exempt advanced therapy medicinal products as are undertaken by the manufacturer's licence holder in accordance with the requirements of the manufacturer's licence, and

(ii) for the handling, control, storage and distribution of the exempt advanced therapy medicinal products which are handled, stored and distributed under the licence, as are necessary to maintain the quality of those products;

(c) inform the licensing authority—

(i) before making any material alteration to the premises or facilities used under the manufacturer's licence, or in the operations for which they are used,

(ii) of any change that manufacturer's licence holder proposes to make to any personnel named in the licence as responsible for quality control of the exempt advanced therapy medicinal products being manufactured or assembled by the manufacturer's licence holder, and

(iii) of any adverse reaction or suspected adverse reaction of which the holder is aware within 15 days of becoming aware of it;

(d) for the purpose of enabling the licensing authority to ascertain whether there are any grounds—

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

(ii) suspending or terminating any licence in accordance with the provisions of Part II of the Act,

permit, and provide all necessary facilities to enable, any person duly authorised in writing by the licensing authority, on production if required of the relevant 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;

(e) ensure that any arrangements that are made with any person for the control, storage and distribution of the exempt advanced therapy medicinal products are adequate to maintain the quality of those products;

(f) not carry out any manufacture or assembly of exempt advanced therapy medicinal products other than—

(i) the manufacture or assembly of those classes of exempt advanced therapy medicinal product specified in the licence, and

(ii) at the premises specified in the licence;

(g) not use any premises for the handling, control, storage or distribution of exempt advanced therapy medicinal products other than those specified in the manufacturer's licence as approved by the licensing authority for that purpose, or approved by the licensing authority for that purpose from time to time;

(h) if using human cells or tissues in an exempt advanced therapy medicinal product, ensure that the donation, procurement and testing of those cells or tissues is in accordance with Directive 2004/23/EC(**24**);

(i) ensure that any human tissue or cell component imported into the United Kingdom and used by the manufacturer's licence holder as a starting material or raw material in the manufacture of an exempt advanced therapy medicinal product shall meet equivalent standards of quality and safety to those laid down in Commission Directives 2006/17/EC(**25**) and 2006/86/EC(**26**);

(j) ensure that any blood or blood component imported into the United Kingdom and used by the manufacturer's licence holder as a starting material or raw material in the manufacture of an exempt advanced therapy medicinal product shall meet equivalent standards of quality and safety to those laid down in Commission Directive 2004/33/EC(**27**), implementing Directive 2002/98/EC(**28**) of the European Parliament and of the Council as regards certain technical requirements for blood and blood components;

(k) where the holder of a manufacturer's licence distributes by way of wholesale dealing any exempt advanced therapy medicinal product manufactured or assembled pursuant to the licence, comply with the requirements of sub-paragraphs (e), (k), (o) and (p) of Schedule 3 as if that person were the holder of a wholesale dealer's licence;

(l) not solicit any order for an exempt advanced therapy medicinal product by—

(i) advertising or making any representation relating to an exempt advanced therapy medicinal product with a view to the advertisement or representation being seen generally by the public in the United Kingdom,

(ii) advertising an exempt advanced therapy medicinal product by means of any catalogue or circular letter,

or otherwise;

(m) at the written request of the licensing authority set up a risk management system designed to identify, characterise, prevent or minimise risks related to the exempt advanced therapy medicinal product;

(n) establish and maintain a system ensuring that the exempt advanced therapy medicinal product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivered to the establishment where the product is used;

(o) subject to paragraph 1(j) of Schedule 2, keep the data referred to in sub-paragraph (n) for a minimum of 30 years after the expiry date of the exempt advanced therapy medicinal product;

(p) secure that the data referred to in sub-paragraph (n) will, in the event that—

(i) the licence is suspended, revoked or withdrawn, or

(ii) the licence holder becomes bankrupt or insolvent,

be held available to the licensing authority by the holder of a manufacturer's licence for the period described in sub-paragraph (o) or such longer period as may be required pursuant to paragraph 1(j) of Schedule 2;

(q) where an exempt advanced therapy medicinal product contains human cells or tissues, ensure that the traceability system established in accordance with subparagraph (n) is

(**24**) OJ No. L 102, 7.4.2004, p.48.
(**25**) OJ No. L 38, 9.2.2006, p.40.
(**26**) OJ No. L 294, 25.10.2006, p.32.
(**27**) OJ No. L 91, 30.3.2004, p.25.
(**28**) OJ No. L 33, 8.2.2003, p.30.

complementary to and compatible with the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC(**29**) as regards human cells and tissues other than blood cells, and Articles 14 and 24 of Directive 2002/98/EC as regards human blood cells; and

(r) not import or export any exempt advanced therapy medicinal product.

SCHEDULE 2

Regulation 3(2)

Standard provisions for manufacturer's licences insofar as those licences relate to exempt advanced therapy medicinal products

1. The holder of a manufacturer's licence must—

(a) place the quality control system referred to in Article 11(1) of Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and for investigational medicinal products for human use(**30**) under the authority of the person notified as being responsible for quality control to the licensing authority in accordance with paragraph 7(2) of Schedule 1 to the Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Regulations 1971(**31**) as being responsible for quality control;

(b) provide such information as may be requested by the licensing authority about—

(i) the products currently being manufactured or assembled under the licence, and

(ii) the operations being carried out in relation to such manufacture or assembly;

(c) inform the licensing authority of any change that the holder proposes to make to any personnel named in the licence as respectively—

(i) responsible for supervising the production operations,

(ii) in charge of the animals from which are derived any substances used in the production of the exempt advanced therapy medicinal products being manufactured or assembled, or

(iii) responsible for the culture of any living tissues used in the manufacture of the exempt advanced therapy medicinal products being manufactured or assembled;

(d) keep readily available for—

(i) inspection by a person authorised by the licensing authority, the batch documentation referred to in Article 9(1) of Commission Directive 2003/94/EC and permit the person authorised to take copies or make extracts from such documentation,

(ii) examination by a person authorised by the licensing authority, the samples of each batch of finished relevant medicinal product referred to in Article 11(4) of Commission Directive 2003/94/EC,

(iii) examination by a person authorised by the licensing authority, durable records of the details of manufacture of any intermediate products held by them which are for use in the manufacture of exempt advanced therapy medicinal products, and these records must—

(aa) be in such form as to ensure that the licence holder has a comprehensive record of all matters that are relevant to an evaluation of the safety, quality

(**29**) OJ No. L 102, 7.4.2004, p.48.
(**30**) OJ No. L 262, 14.10.2003, p.22.
(**31**) S.I. 1971/974. There are no relevant amendments.

and efficacy of any finished exempt advanced therapy medicinal products which the holder manufactures using those intermediate products, and

(bb) not be destroyed without the consent of the licensing authority until the records of the details of manufacture of any finished medicinal products which were or may be manufactured using those intermediate products may be destroyed in accordance with the requirements of these Regulations;

(e) if so directed by the licensing authority, withhold, so far as may be reasonably practicable, a batch from distribution for such period not exceeding six weeks as may be specified by the licensing authority, where the licence holder has been informed by the licensing authority that the batch of the exempt advanced therapy medicinal product has been found not to conform as regards strength, quality or purity with—

(i) the specification of the exempt advanced therapy medicinal product, or

(ii) the provisions of these Regulations, the Act or any other regulations under the Act that are applicable to the exempt advanced therapy medicinal product;

(f) ensure that any tests for determining conformity with the standards and specifications applying to any particular product used in the manufacture of an exempt advanced therapy medicinal product must, except so far as the conditions of the product specification for that product otherwise provide, be applied to samples taken from the exempt advanced therapy medicinal product after all manufacturing processes have been completed, or at such earlier stage in the manufacture as may be approved by the licensing authority;

(g) take all reasonable precautions and exercise all due diligence to ensure that any information the licence holder provides to the licensing authority which is relevant to an evaluation of the safety, quality or efficacy of—

(i) any exempt advanced therapy medicinal product for human use which the licence holder manufactures or assembles, or

(ii) any starting materials or intermediate products that the licence holder holds which are for use in the manufacture of exempt advanced therapy medicinal products,

is not false or misleading in any material particular;

(h) ensure that the container of the exempt advanced therapy medicinal product shall be labelled to show the following particulars—

(i) the name of the exempt advanced therapy medicinal product,

(ii) the expiry date in clear terms including the year and month and, if applicable, the day,

(iii) a description of the active substance, expressed qualitatively and quantitatively,

(iv) where the product contains cells or tissues of human or animal origin—

(aa) a statement that the product contains such cells or tissues,

(bb) a short description of the cells or tissues and of their specific origin,

(v) the pharmaceutical form and the contents by weight, volume or number of doses of the product,

(vi) a list of excipients, including preservative systems,

(vii) the method of use, application, administration or implantation and the route of administration and space provided for the prescribed dose to be indicated,

(viii) any special storage precautions,

(ix) specific precautions relating to the disposal of the unused product or waste derived from the product and, where appropriate, reference to any appropriate collection system,

(x) the name and address of the manufacturer's licence holder,

(xi) the manufacturer's licence number,

(xii) the manufacturer's batch number,

(xiii) the unique donation code referred to in Article 8(2) of Directive 2004/23/EC, and

(xiv) where the exempt advanced therapy medicinal product is for autologous use, the unique patient identifier and the wording "For autologous use only"; and

(i) ensure that the package leaflet of the exempt advanced therapy medicinal product shall include the following particulars—

(i) the name of the exempt advanced therapy medicinal product,

(ii) the intended effect of the medicinal product if correctly used, applied, administered or implanted,

(iii) where the product contains cells or tissues of human or animal origin—

(aa) a statement that the product contains such cells or tissues,

(bb) a short description of the cells or tissues and, where such cells or tissues are of animal origin, their specific origin,

(iv) where the product contains a medical device or an active implantable medical device, a description of that device and, where that device contains cells or tissues of animal origin, their specific origin,

(v) any necessary instructions for use, including—

(aa) the posology,

(bb) the method of use, application, administration or implantation and, if appropriate, the route of administration,

(cc) a description of symptoms of overdose,

(dd) action to be taken in the event of overdose, including any emergency procedures,

(ee) action to be taken if one or more doses have been missed, and

(ff) a recommendation to consult the doctor or pharmacist, for any clarification on the use of the product,

(vi) where adverse reactions are known, a description of those which may occur under recommended conditions of use of the product and, if appropriate, an indication of action to be taken in such a case,

(vii) an instruction that the patient report any adverse reaction not specified in the package leaflet to the doctor or pharmacist,

(viii) the expiry date and a warning against using the product after that date,

(ix) any special storage precautions,

(x) a description of any visible signs of deterioration,

(xi) a complete qualitative and quantitative composition,

(xii) the name and address of the manufacturer's licence holder, and

(xiii) the date on which the package leaflet was last revised; and

(j) keep the data referred to in sub-paragraph (n) of Schedule 1 for such period, being a period of longer than 30 years, as may be specified by the licensing authority.

2. The manufacturer's licence holder may use a contract laboratory pursuant to Article 11(2) of Commission Directive 2003/94/EC if operated by a person approved by the licensing authority.

SCHEDULE 3

Regulation 3(3)

Requirement that holders of wholesale dealer's licences comply with certain obligations in relation to exempt advanced therapy medicinal products

The holder of a wholesale dealer's licence, must—

(a) at all times have at that person's disposal the services of a person (referred to in this Schedule as "a responsible person") who—

(i) in the opinion of the licensing authority—

(aa) 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

(bb) has experience in those procedures and activities which is adequate for those purposes, and

(ii) is responsible for ensuring, in relation to exempt advanced therapy medicinal products, compliance with the conditions of the wholesale dealer's licence;

(b) notify the licensing authority of—

(i) the name and address and degrees, diplomas or qualifications and experience of the person who will carry out the functions of responsible person,

(ii) any change of responsible person;

(c) subject to sub-paragraph (d), not permit any person to act as responsible person other than the person named in the licence as responsible person or, any other such person whose name is notified to the licensing authority in accordance with sub-paragraph (b)(ii);

(d) not permit a person to act as a responsible person where the licence holder has been notified in writing by the licensing authority that it is of the opinion that—

(i) the person so acting does not satisfy the provisions of sub-paragraph (a) as respects qualifications and experience, or

(ii) that person is failing to carry out the duties referred to in sub-paragraph (b) adequately or at all,

provided that the licensing authority has given the licence holder and the person acting as a responsible person the opportunity of making representations to them (orally or in writing) beforehand;

(e) comply with the guidelines on good distribution practice;

(f) provide and maintain such staff, premises, equipment and facilities for the handling, storage and distribution of the exempt advanced therapy medicinal products which are handled, stored or distributed under the licence as are necessary to maintain the quality of, and ensure proper distribution of, the exempt advanced therapy medicinal products which are handled, stored or distributed pursuant to the licence;

(g) inform the licensing authority of any proposed structural alteration to, or discontinuance of use of, premises to which the licence relates or premises which have been approved from time to time by the licensing authority;

(h) for the purpose of enabling the licensing authority to ascertain whether there are any grounds—

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

(ii) for suspending or terminating any licence in accordance with the provisions of Part II of the Act,

permit and provide all necessary facilities to enable any person duly authorised in writing by the licensing authority, on production if required of the relevant 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;

(i) obtain supplies of exempt advance therapy medicinal products only from a—

(i) manufacturer's licence holder, or

(ii) wholesale dealer's licence holder,

in respect of such products;

(j) distribute an exempt advanced therapy medicinal product by way of wholesale dealing only to—

(i) a holder of a wholesale dealer's licence relating to those products; or

(ii) a person who—

(aa) may lawfully administer those products, and

(bb) solicited the product for an individual patient;

(k) establish and maintain a system ensuring that the exempt advanced therapy medicinal product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the establishment where the product is used;

(l) keep such records containing the following information in relation to exempt advanced therapy medicinal products which are received or dispatched by the holder of the wholesale dealer's licence—

(i) the date of receipt or, as the case may be, dispatch,

(ii) the name of the products,

(iii) the quantity of the product 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;

(m) have in place a plan for recalling, in cooperation with the manufacturer, any advanced therapy medicinal product where such recall is ordered by the licensing authority;

(n) inform the licensing authority of any adverse reaction to any exempt advanced therapy medicinal product supplied by the holder of the wholesale dealer's licence of which the holder is aware;

(o) subject to sub-paragraph (d) of Schedule 4, keep the data referred to in sub-paragraph (k) for a minimum of 30 years after the expiry date of the exempt advanced therapy medicinal product;

(p) secure that the data referred to in sub-paragraph (k) will, in the event that—

(i) the licence is suspended, revoked or withdrawn, or

(ii) the licence holder becomes bankrupt or insolvent,

be held available to the licensing authority by the holder of a wholesale dealer's licence for the period described in sub-paragraph (o) or such longer period as may be required pursuant to sub-paragraph (d) of Schedule 4;

(q) not import or export any exempt advanced therapy medicinal product; and

(r) not solicit any order for an exempt advanced therapy medicinal product by—

(i) advertising or making any representation relating to an exempt advanced therapy medicinal product with a view to the advertisement or representation being seen generally by the public in the United Kingdom,

(ii) advertising an exempt advanced therapy medicinal product by means of any catalogue or circular letter, or

(iii) any other means.

SCHEDULE 4

Regulation 3(4)

Standard provisions for wholesale dealer's licences insofar as those licences relate to exempt advanced therapy medicinal products

The standard provisions, for the purposes of Part II of the Act, for wholesale dealer's licences insofar as they relate to exempt advanced therapy medicinal products are—

(a) the licence holder shall not use any premises for the purpose of the handling, storage or distribution of exempt advanced therapy medicinal products other than those specified in the licence holder's licence or notified to the licensing authority by the licence holder from time to time and approved by the licensing authority;

(b) the licence holder shall provide such information as may be requested by the licensing authority concerning the type and quantity of any exempt advanced therapy medicinal product which the licence holder handles, stores or distributes;

(c) the licence holder shall take all reasonable precautions and exercise all due diligence to ensure that any information the holder provides to the licensing authority which is relevant to an evaluation of the safety, quality or efficacy of any exempt advanced therapy medicinal product which the holder handles, stores or distributes is not false or misleading in a material particular; and

(d) the licence holder shall keep the data referred to in sub-paragraph (k) of Schedule 3 for such period, being a period of longer than 30 years, as may be specified by the licensing authority.

SCHEDULE 5

Regulation 8

Amendments to the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994

Amendment of regulation 1

1. In regulation 1(2) (citation, commencement and interpretation)—

(a) after the definition of "the Act", insert the following definitions—

""advanced therapy medicinal product" has the meaning set out in paragraph 1(a) of Article 2 of the ATMP Regulation";

""the ATMP Regulation" means Regulation (EC) No. 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products;";

(b) in the definition of "the 2001 Directive"(**32**), for "and the Paediatric Regulation" substitute—

"

the Paediatric Regulation,

the ATMP Regulation,

Directive 2008/29/EC of the European Parliament and of the Council,

Directive 2009/53/EC of the European Parliament and of the Council, and

Commission Directive 2009/120/EC;";

(c) in the definition of "Regulation (EC) No. 726/2004"(**33**), after "as amended by the Paediatric Regulation" insert "and the ATMP Regulation"; and

(d) in the definition of "the relevant Community provisions"(**34**)—

(i) delete the word "and", and

(ii) after "the Paediatric Regulation;" insert—

"and the ATMP Regulation;".

Amendment of Schedule 1

2. In Schedule 1 (exemptions and exceptions from the provisions of regulation 3), in paragraph 2(b), delete ", price list ".

Amendment of Schedule 3

3.—(1) Schedule 3 (offences, penalties etc) shall be amended as follows.

(2) After paragraph 10A(**35**), insert the following paragraphs—

"**10B.**—(1) A holder of a Community marketing authorization for an advanced therapy medicinal product who fails to—

(a) submit an additional report evaluating the effectiveness of a risk management system and the results of studies within 21 days of receipt of a request made under sub-paragraph (2) of Article 14(2) of the ATMP Regulation or such longer period as the European Medicines Agency may specify; or

(b) include an evaluation of the effectiveness of a risk management system or the results of any study performed pursuant to sub-paragraph (3) of Article 14(2) of the ATMP Regulation,

shall be guilty of an offence.

(2) Any relevant person who fails—

(a) to establish a traceability system in accordance with the requirements set out in Article 15(1) of the ATMP Regulation;

(b) where the product contains human cells or tissues, to ensure that the traceability system is complementary to and compatible with, the requirements laid down in Articles 8 and 14 of Directive 2004/23/EC as regards human cells and tissues

(**32**) The definition of "the 2001 Directive" was inserted by S.I. 2002/236 and amended by S.I. 2003/2321, 2004/3224, 2005/50, 2005/2759 and 2008/3097.
(**33**) The definition of "the Regulation (EC) No 726/2004" was inserted by S.I. 2004/3224 and amended by S.I. 2008/3097.
(**34**) The definition of "the relevant Community provisions" was substituted by S.I. 2002/236 and amended by S.I. 2003/2321, 2004/3224, 2005/2759 and 2008/3097.
(**35**) Paragraph 10A was inserted by S.I. 2005/1710.

other than blood cells, and Articles 14 and 24 of Directive 2002/98/EC(**36**) as regards blood cells; or

(c) to keep the data to which the traceability system relates in accordance with the requirements set out in Article 15(4) of the ATMP Regulation,

shall be guilty of an offence.

(3) In sub-paragraph (2), "relevant person" means a person—

(a) who is the holder of a Community marketing authorization for an advanced therapy medicinal product, or

(b) whose Community marketing authorization for an advanced therapy medicinal product has been suspended, revoked or withdrawn.".

(3) In paragraphs 11 and 12(**37**), after "Directive" (in each place that it occurs) insert ", of Chapter 4 of the ATMP Regulation".

(4) After paragraph 13B(**38**), insert the following paragraphs—

"**13C.**—(1) Subject to sub-paragraphs (2) and (3), any person who is or, immediately before its revocation or suspension, was the holder of a marketing authorisation relating to an advanced therapy medicinal product who fails to—

(a) keep the data referred to in Article 15(1) of the ATMP Regulation for 30 years after the expiry date of the product or such longer period as may be required by the Commission; or

(b) transfer the data referred to in Article 15(1) to the European Medicines Agency established by Regulation (EC) No. 726/2004 in the event of that person's bankruptcy or liquidation,

shall be guilty of an offence.

(2) Sub-paragraph (1)(b) does not apply if—

(a) the person is bankrupt or in liquidation and has transferred the data to another person; or

(b) the period for which the person was required to keep the data pursuant to sub-paragraph (1)(a) has expired.".

(5) In paragraph 15(**39**) (miscellaneous), for "or 10A" substitute ", 10A or 10B".

Amendment of Schedule 6

4. In Schedule 6 (transitional provisions), after paragraph 5 insert the following paragraph—

"**6.**—(1) Subject to sub-paragraph (2), these Regulations shall not apply to advanced therapy medicinal products which were legally on the European Union market on 30th December 2008 until 30th December 2011.

(2) These Regulations shall not apply to advanced therapy medicinal products which are tissue engineered products which were legally on the Community market in accordance with national or Community legislation on 30th December 2008 until 30th December 2012.".

(**36**) OJ No. L33, 8.2.2003, p.30.
(**37**) Paragraph 12 was amended by S.I. 1998/3105 and S.I. 2002/236.
(**38**) Paragraph 13B was inserted by S.I.2008/3097.
(**39**) Paragraph 15 was amended by S.I.2005/1710.

EXPLANATORY NOTE

(This note is not part of the Regulations)

These Regulations provide for the enforcement of Regulation (EC) No.1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products ("ATMPs").

Regulation 2 disapplies section 7 of the Medicines Act 1968 (which is concerned with product licences for medicinal products which are not subject to the European Union law governing medicines) in relation to exempt ATMPs.

Regulation 3 gives effect to—

(a) Schedule 1 which sets out requirements which have effect as provisions of manufacturers' licences insofar as they relate to exempt ATMPs;

(b) Schedule 2 which sets out requirements which may be incorporated in manufacturers' licences insofar as they relate to exempt ATMPs;

(c) Schedule 3 which sets out requirements which have effect as provisions of wholesale dealers' licences insofar as they relate to exempt ATMPs; and

(d) Schedule 4 which sets out requirements which may be incorporated in wholesale dealers' licences insofar as they relate to exempt ATMPs.

Regulation 4 makes it an offence to treat a patient with an ATMP if there is not a system of patient and product traceability. It is a defence to that offence if the person is assured in writing that there is such a system in relation to the treatment. A person commits an offence if they provide such a written assurance when there is not a system in place in relation to such treatment.

Regulation 5 makes provision as to data relating to starting and raw materials of exempt ATMPs including substances coming into contact with the cells or tissues that exempt ATMPs may contain. It subjects a holder of a manufacturing licence in respect of an exempt ATMP to liability for a criminal offence if that person does not keep data required as part of a traceability system for 30 years or, in the event of that person's bankruptcy or liquidation, transfer it to the licensing authority.

Regulation 6 amends the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 so that they do not apply in relation to exempt ATMPs.

Regulation 7 amends the Medicines (Applications for Manufacturer's and Wholesale Dealer's Licences) Regulations 1971 so that an applicant for a manufacturer's licence which relates to exempt ATMPs must provide an outline of the arrangements for maintaining records to allow product traceability containing sufficient detail to enable linking a product to the patient who received it and vice versa.

Regulation 8 and Schedule 5 amend the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 to enable enforcement of the provisions of Regulation (EC) No 1394/2007 (other than in relation to exempt ATMPs).

They also give effect to the decision of the European Court of Justice in *C-143/06 Ludwigs-Apotheke München Internationale Apotheke v Juers Pharma Import-Export GmbH* by permitting price lists to be issued that do not make representations in respect of a 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 that person's individual patients on that person's direct personal responsibility, in order to fulfil the special needs of those patients. They also make an amendment to take into account an amendment to Directive 2001/83 of the European Parliament and of the Council by Commission Directive 2009/120/EC.

Regulation 9 amends the Medicines for Human Use (Clinical Trials) Regulations so that the procedures for giving an ethics committee opinion and for authorising clinical trials apply to trials involving tissue engineered products in the same way that they apply to trials involving gene therapy and somatic cell therapy. It also corrects an error in Schedule 2 to those Regulations.

Regulation 10 amends the Medicines for Human Use (Manufacturing, Wholesale Dealing and Miscellaneous Amendments) Regulations 2005 so that they do not apply to ATMPs. It also gives effect to the decision of the European Court of Justice in *C-143/06* by permitting holders of wholesale dealer's licences or manufacturer's licences to issue price lists that do not make representations in respect of a product to which paragraph 1 of Schedule 1 to the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994.

These Regulations (other than the amendment resulting from Commission Directive 2009/120) have been notified to the European Commission and other Member States of the European Union in accordance with Directive 98/34/EC(**40**) of the European Parliament and of the Council laying down a procedure for the provision of information in the field of technical standards and regulations and rules on Information Society services, as amended by Article 1(4) of the European Parliament and Council Directive 98/48/EC(**41**) and Council Directive 2006/96/EC of 20 November 2006(**42**).

An Impact Assessment has been prepared in respect of these Regulations which is available from the Medicines and Healthcare products Regulatory Agency, Market Towers, 1 Nine Elms Lane, London SW8 5NQ.

(**40**) OJ No. L204, 21.7.1998, p.37.
(**41**) OJ No. L217, 5.8.1998, p.18.
(**42**) OJ No L.363, 20.12.2006, p.81.