

## **REGULATION (EC) NO 1394/2007 ON ADVANCED THERAPY MEDICINAL PRODUCTS (“THE ATMP REGULATION”)**

### **GUIDANCE ON THE UK’S ARRANGEMENTS UNDER THE HOSPITAL EXEMPTION SCHEME**

#### **PURPOSE OF THIS GUIDANCE**

1. This guidance has been developed by the Medicines and Healthcare products Regulatory Agency (MHRA) and aims to clarify the arrangements that will apply in the UK under the hospital exemption scheme under the ATMP Regulation and laid down in Article 3 (7) of Directive 2001/83/EC. In July 2008, the MHRA consulted on the proposed arrangements that will apply under the scheme and consulted on draft guidance in July 2009. The UK’s legislation for implementing the ATMP Regulation including the requirements that apply under the hospital exemption scheme was laid in Parliament on 26 July 2010 and came into force on 19 August 2010.

#### **SCOPE**

2. This guidance outlines the requirements that will apply to advanced therapy medicinal products (ATMPs) made and used under the hospital exemption scheme in the UK. The guidance does not apply to ATMPs that will be authorised under the ATMP Regulation, for which the centralised marketing authorisation procedure will apply, nor does it apply to ATMPs supplied as investigational ATMPs for use in a clinical trial. The guidance provides an explanation of the relationship between the hospital exemption scheme and ATMPs that may be supplied under the UK’s national scheme under Article 5 (1) of Directive 2001/83/EC<sup>1</sup> (that is, “specials” manufactured in the UK or notified to MHRA under the import notification scheme).

#### **INTRODUCTION AND CONTEXT TO THE EXEMPTION**

3. The ATMP Regulation entered into force on 30 December 2007 and applied from 30 December 2008. The UK’s legislation for implementing the Regulation and the requirements that will apply under the hospital exemption came into force on 19 August 2010.

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<sup>1</sup> Article 5 (1) of Directive 2001/83/EC provides that “a Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility”.

4. Under the ATMP Regulation, those medicinal products which come within the scope of Directive 2001/83/EC and are categorised as ATMPs are to be regulated under the centralised European procedure. Under this procedure, a centralised European marketing authorisation is granted by the European Commission following assessment by the European Medicines Agency (EMA).
5. Under Article 3 (7) of 2001/83/EC, there is an exemption from central authorisation for ATMPs which are prepared on a non routine basis and used within the same Member State in a hospital in accordance with a medical prescription for an individual patient. The exemption was included in the Regulation in recognition of the small scale and developmental nature of activity carried out in some hospitals, which argued for a degree of flexibility over the nature of regulatory requirements. Member States are required to implement this Community requirement for a hospital exemption by putting in place arrangements at national level to meet the specific requirements set out in the Regulation. The MHRA is responsible for the regulatory arrangements under the exemption in the UK.

#### **REQUIREMENTS UNDER THE EXEMPTION**

6. The Regulation stipulates that manufacture of ATMPs under the hospital exemption must be authorised by the Member State (the MHRA in the UK). In addition, traceability, quality and pharmacovigilance standards for ATMPs made under the exemption must be equivalent to ATMPs for which a centralised market authorisation would be granted by the EMA. The text for the exemption reads:

***Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.***

***Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.***

## THE RELATIONSHIP BETWEEN THE HOSPITAL EXEMPTION AND ARTICLE 5 (1) OF DIRECTIVE 2001/83/EC

7. Although the two schemes are legally distinct, there are some apparent similarities between the kind of activities falling within the hospital exemption and the UK “specials” scheme set up under the derogation permitted in Article 5 (1) of Directive 2001/83/EC. Products made or supplied under either scheme are referred to as “unlicensed” since there is no product licence (marketing authorisation). However, each site will need to hold a manufacturer’s licence of a type specific to the scheme. It should be noted that a qualified person (QP) is not required for either scheme. The UK “specials” scheme, including the linked import notification scheme, permits doctors and certain other prescribers to commission an unlicensed relevant medicinal product to meet the special needs of individual patients. In principle this latter scheme would be available for ATMPs as for any other category of medicinal product. The MHRA expects that there may in practice be a variety of situations in which small scale production of an unlicensed ATMP is envisaged to meet requests made by a prescriber. In these circumstances operators will need to consider carefully which of the two schemes, (if either), is applicable.
8. MHRA advice to operators who are uncertain about which of the two schemes may be applicable is as follows:
- Check this guidance to identify the main conditions relating to the hospital exemption and check *MHRA’s Guidance Note 14: The supply of unlicensed relevant medicinal products for individual patients* to identify the requirements of the “specials” scheme.
  - Seek advice from the MHRA about which scheme is applicable.

<b>Summary of some of the main differences in scope between the hospital exemption and “specials” schemes</b>	
<b>Hospital exemption</b>	<b>The “specials” scheme</b>
The ATMP must be prepared and used in the same EU Member State	Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK
The ATMP must be commissioned by a medical practitioner	Products can be prescribed by doctors, dentists and supplementary prescribers
The ATMP must be custom made to meet an individual prescription and preparation must be on a “non- routine basis”	There is a special needs test (interpreted to mean the absence of a pharmaceutically equivalent and available licensed product)
The ATMP must be used in a hospital	There is no stipulation as to location

9. There are also currently significant differences in the regulatory requirements relating to products coming within the scope of the two schemes. This guidance sets out the requirements relating to good manufacturing practice, pharmacovigilance, traceability and patient information under the hospital exemption. Requirements relating to the “specials” scheme are not identical and are set out in Guidance Note 14. Following proposals set out in consultation document MLX 353, the MHRA intends to bring forward proposals relating to those ATMPs that come within the “specials” scheme. The intention is that for ATMPs that are “specials” requirements relating to good manufacturing practice, pharmacovigilance and traceability will be aligned with the requirements under the hospital exemption. This is to ensure that regulatory provisions for ATMPs reflect the particular characteristics of ATMPs, not least the public health risks posed, and also to minimise unnecessary discontinuities in regulation where activity relating to ATMPs transfers from one regulatory scheme to another. Further information will be published on the MHRA website in due course.
10. A flow chart is attached at **Annex A** which illustrates how the hospital exemption fits with wider provisions of medicines legislation. The issue has been raised as to what constitutes “non routine” preparation of an ATMP under the hospital exemption scheme. The MHRA considers that it is not feasible to provide a simple numerical formula that would delineate the boundary between routine and non routine production. The Agency has produced some guidance which includes some pointers as to factors that should be considered and this is at **Annex B**.
11. The Human Tissue Authority (HTA) regulates the use of tissues and cells for human application. Under the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the following activities must be carried out under the authority of an HTA licence: consent, donor selection, donor testing, procurement (collection), processing, storage, distribution and import and export. In the case of ATMPs the HTA regulates the donation (i.e. consent, donor selection and testing), procurement and testing of tissues and cells used in the manufacture of ATMPs. The manufacturing process following procurement and removal of tissues and cells from a tissue bank is regulated by the MHRA.

## **STANDARDS THAT ARE REQUIRED UNDER THE HOSPITAL EXEMPTION**

### **Good manufacturing practice (GMP) and quality**

12. Under the Regulation, there is a requirement for manufacture under the hospital exemption to be authorised by the competent authority of the Member State. In the UK a manufacturer will be required to obtain a manufacturer’s licence from the MHRA. The licence will authorise the manufacture of particular categories of ATMPs (gene therapy, somatic

cell therapy or tissue engineered product) rather than individual products in line with current manufacturer's licensing arrangements. ATMPs made and used under the exemption must comply with the principles of GMP. In addition, the European Commission will issue GMP guidelines that will be specific to ATMPs - these will be in Annex 2 of EU GMP and are currently being revised. The MHRA will inspect for compliance with GMP which will be applied appropriately to the nature of the products involved. Inspections will be risk-based and in accordance with Hampton principles.

### **Pharmacovigilance**

13. Manufacturers operating under the hospital exemption will be required to record any adverse reactions to an ATMP and notify the MHRA of any suspected serious adverse reactions. At the point that a manufacturer's licence is sought to operate under the exemption, the MHRA will consider whether a risk management plan is necessary and may request one from the manufacturer. The MHRA may also ask for a risk management plan from the manufacturer at any point. The risk management plan should provide details of the system in place to identify, characterise and minimise any risks related to the product. The clinician/medical practitioner using the ATMP will be required to record all adverse reactions and report serious adverse reactions to the MHRA.

### **Traceability**

14. The traceability provisions that will apply include compliance with the requirements laid down in Article 15 of the ATMP Regulation as well as the traceability requirements under the Tissues and Cells Directive (2004/23/EC) and the Blood Directive (2002/98/EC). Manufacturers of ATMPs must comply with those requirements. The hospital in which the ATMP is used will be required to establish and maintain a system for patient and product traceability containing sufficient detail to enable traceability between recipients of ATMPs and donors of the tissues and cells used in their manufacture.
15. In the case of bankruptcy, responsibility for holding the traceability data for 30 years in respect of centrally authorised ATMPs would lie with the EMA. In the case of bankruptcy for ATMPs made and used under the exemption, it would be a condition of operating under the scheme that arrangements are put in place by the manufacturer and hospital for the data to be transferred to the MHRA in the event of a cessation of operations.

## **REPORTING REQUIREMENTS**

16. Manufacturers operating under the hospital exemption will be required to make an annual return to the MHRA. This return must set out the

activities that are being carried out under the scheme. This must include a description and number of batches and units manufactured in each of the three categories of ATMPs for which a manufacturer's licence has been granted. This return will inform risk based inspection in line with Hampton and better regulation principles. Monitoring arrangements will enable the MHRA to ensure the new scheme is working within the required parameters.

## **SANCTIONS AND PENALTIES**

17. Breaching the conditions applicable to the hospital exemption will mean that an organisation or individual could be liable to sanctions on the basis of placing a relevant medicinal product on the market without a marketing authorisation. Sanctions and penalties that apply to other categories of medicines under the centralised authorisation procedure would also apply to centrally authorised ATMPs.

## **REQUIREMENTS IN RESPECT OF WHOLESALE DEALERS**

18. The holder of a wholesale dealer's licence must comply with certain obligations in relation to the wholesale distribution of exempt ATMPs. Distribution of exempt ATMPs may only be carried out by the holder of the manufacturer's licence who manufactured the products or by the holder of a wholesale dealer's licence. Licence holders will be required to maintain records for the purposes of traceability for a period of 30 years. Import or export of exempt ATMPs is not permitted: the exemption is restricted to an ATMP made and used in the same Member State.

## **OTHER REQUIREMENTS NOT SPECIFIED WITHIN THE REGULATION BUT WHICH WILL APPLY UNDER THE EXEMPTION IN THE UK**

19. The specific parameters that are laid down in the ATMP Regulation for the exemption are intended to ensure minimum standards. As outlined in the consultation document issued in July 2008, the MHRA has considered whether additional provisions are necessary and considers that requirements in respect of patient information and advertising are necessary under the exemption.

### **Labelling**

20. Manufacturers operating under the hospital exemption will be required to provide the following information in the labelling of the ATMP:
  - (a) The name of the exempt advanced therapy medicinal product;
  - (b) A description of the active substance(s) expressed qualitatively and quantitatively, including, where the product contains cells or tissues, the statement: "This product contains cells of human/animal [as appropriate] origin" together with a short

description of these cells or tissues and of their specific origin, including the species of animal in cases of non human origin;

- (c) The pharmaceutical form and, if applicable, the contents by weight, by volume or by number of doses of the product;
- (d) A list of excipients, including preservative systems;
- (e) The method of use, application, administration or implantation and, if necessary, the route of administration. If applicable, space shall be provided for the prescribed dose to be indicated;
- (f) A special warning that the medicinal product must be stored out of the reach and sight of children;
- (g) Any special warning necessary for the particular medicinal product;
- (h) The expiry date in clear terms (month and year; and day if applicable);
- (i) Special storage precautions, if any;
- (j) Specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place;
- (k) The name and address of the manufacturer;
- (l) Manufacturing authorisation number;
- (m) The manufacturer's batch number and the unique donation and product codes referred to in Article 8 (2) of Directive 2004/23/EC;
- (n) In the case of advanced therapy medicinal products for autologous use, the unique patient identifier and the statement "For autologous use only".

#### **Package leaflet requirements**

21. Manufacturers operating under the hospital exemption will be required to provide the following information in the package leaflet.

- (a) The name of the exempt advanced therapy medicinal product;
- (b) An indication of what the product is to be used to treat;

- (c) Where the product contains cells or tissues of human or animal origin -
  - (i) a statement that the product contains such cells or tissues,
  - (ii) a short description of the cells or tissues and, where such cells or tissues are of animal origin, their specific origin;
- (d) 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;
- (e) Any necessary instructions for use, including -
  - (i) the posology
  - (ii) the method of use, application, administration or implantation and, if appropriate, the route of administration,
  - (iii) a description of symptoms of overdose,
  - (iv) action to be taken in the event of overdose, including any emergency procedures,
  - (v) action to be taken if one or more doses have been missed, and
  - (vi) a recommendation to consult the doctor or pharmacist, for any clarification on the use of the product;
- (f) 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;
- (g) An instruction that the patient report any adverse reaction which is not mentioned in the leaflet to his doctor or pharmacist;
- (h) A reference to the expiry date indicated on the label, with:
  - (i) a warning against using the product after that date,
  - (ii) any special storage precautions, and
  - (iii) a description of any visible signs of deterioration;
- (i) A complete qualitative and quantitative composition;



- (j) The name and address of the manufacturer; and
- (k) The date on which the package leaflet was last revised.

### **Advertising**

- 22. Manufacturers operating under the exemption will not be permitted to advertise specific ATMPs made and used under the exemption. It will be permissible to advertise the service that is provided (for example manufacture of certain categories of ATMPs) but it will not be acceptable for specific ATMPs to be advertised. This does not prohibit the circulation of a simple list of products and prices, provided no medicinal claims are made.

### **Ethical issues**

- 23. No new legislative requirements are proposed in respect of ethical issues for ATMPs made and used under the exemption. Provided it does not involve xenotransplantation (which, under current Department of Health guidance should be presented, conducted and managed as research), and is not otherwise in the context of research, administering an ATMP as part of a patient's clinical treatment would not require a favourable research ethics committee opinion. Clinical ethical issues presented by using ATMPs in clinical practice would be covered by the NHS trusts' clinical governance arrangements. Further guidance can be found at

[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_063075](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063075) and

[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4005727](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005727).

## **FURTHER INFORMATION AND CONTACTS AT MHRA**

- 24. Further information including Q&A material about the ATMP Regulation is available on the MHRA website (<http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/index.htm> ). Specific requests for guidance about whether a product would fall under the UK's hospital exemption scheme should be directed to the MHRA's Borderline Unit in the first instance (<http://www.mhra.gov.uk/Howweregulate/Medicines/Doesmyproductneedalicense/Borderlineproducts/index.htm> ).
- 25. Requests for scientific advice on products which are likely to be authorised under the ATMP Regulation should be directed to the EMA (<http://www.emea.europa.eu/>). Scientific advice can also be requested from the MHRA. Further information about obtaining scientific advice from MHRA can be found at <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedic>

[ines/Informationforlicenceapplicants/Otherusefulservicesandinformation/Scientificadviceforlicenceapplicants/CON009534](#) .

26. This guidance should not be taken as a complete or definitive statement of the law, which may only be given by the Courts. It is not intended as a substitute for legal or other professional advice. The responsibility remains with the operator to ensure they are clear on the regulatory position of products which are, or may be, ATMPs and to seek the necessary advice.