GUIDANCE ON THE UK'S HOSPITAL EXEMPTION SCHEME FOR ADVANCED THERAPY MEDICINAL PRODUCTS.

PURPOSE OF THIS GUIDANCE AND SCOPE

1. This guidance has been developed by the Medicines and Healthcare products Regulatory Agency (MHRA) and aims to clarify the requirements and arrangements that apply to advanced therapy medicinal products (ATMPs) made and used under the hospital exemption scheme in the UK which is contained in the Human Medicines Regulation 2012.

2. The guidance does not apply to ATMPs that will be authorised under a marketing authorisation, nor does it apply to ATMPs supplied as investigational ATMPs for use in a clinical trial.

3. The guidance provides an explanation of the relationship between the hospital exemption scheme and ATMPs that may be supplied under the UK's national "Specials" scheme (that is, "specials" manufactured in the UK or notified to MHRA under the import notification scheme).

THE RELATIONSHIP BETWEEN THE HOSPITAL EXEMPTION SCHEME AND SPECIALS SCHEME

4. Although the hospital exemption scheme and UK "Specials" scheme are legally distinct, there are some apparent similarities between the kind of activities falling under either scheme. 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.

5. 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.

Summary of some of the main differences in scope between the hospital exemption and "specials" schemes	
Hospital exemption	**The "specials" scheme**
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

6. 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.

7. 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

8. There is a requirement for manufacture under the hospital exemption to be authorised. A manufacturer is 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. 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

9. 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

10. Manufacturers must 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. Where an exempt advanced therapy medicinal product contains human cells or tissues, ensure that the traceability system established in accordance with paragraph 8 is complementary to and compatible with the requirements imposed pursuant to—

    (a) as regards gametes and embryos, sections 12(3), and 33A to 33D of, and paragraph 1 of Schedule 3A to, the Human Fertilisation and Embryology Act 1990;

    (b) as regards blood cells, regulations 8, 9(e) and 14 of the Blood Safety and Quality Regulations 2005; and

    (c) as regards other cells and tissues, regulations 13 and 16 of, and paragraph 1 of Schedule 2 to, the Human Tissue (Quality and Safety for Human Application) Regulations 2007

    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.

11. In the case of bankruptcy for ATMPs made and used under the exemption, it is 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

12. 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 a risk-based inspection Monitoring arrangements will enable the MHRA to ensure the new scheme is working within the required parameters.

SANCTIONS AND PENALTIES

13. 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

14. 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 UK .

OTHER REQUIREMENTS WHICH WILL APPLY UNDER THE HOSPITAL EXEMPTION IN THE UK

Labelling

15. 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 assigned by a tissue establishment pursuant to—

(i) paragraph 1 of Schedule 3A to the Human Fertilisation and Embryology Act 1990, as regards human gametes and embryos; and

(ii) paragraph 1 of Schedule 2 to the Human Tissue (Quality and Safety for Human Application) Regulations 2007, as regards other human tissues and cells]

(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

16. 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

17. 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

18. Provided it does not involve xenotransplantation (which, under current Department of Health and Social Care 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 INFORMATION AND CONTACTS AT MHRA

19. Further information including Q&A material about the ATMP Regulation is available on the MHRA website

    https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing

20. 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

    https://www.gov.uk/guidance/decide-if-your-product-is-a-medicine-or-a-medical-device

21. Scientific advice can be requested from the MHRA. Further information about obtaining scientific advice from MHRA can be found at

    https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra

22. 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.