Guidelines for the Blood Transfusion Services

Annexe 6: Advanced Therapy Medicinal Products (ATMPs)

http://www.transfusionguidelines.org/red-book/annex-6-advanced-therapy-medicinal-products-atmps

Annexe 6:

Advanced Therapy Medicinal Products (ATMPs)

An Advanced Therapy Medicinal Product(ATMP) is a medicinal product which is either:

- a gene therapy medicinal product
- a somatic cell therapy medicinal product
- a tissue engineered product

ATMPs are governed by UK medicines legislation. ATMPs are currently available under four routes: via marketing authorisation; via clinical trial authorisation; via unlicensed use either through hospital exemption, on a non-routine basis, or for an individual patient with a special clinical need under the ‘specials’ scheme.

Legislation around ATMPs include: the Human Medicines Regulations 2012 SI 2012/1916, setting the rules for marketing authorisation and pharmacovigilance, hospital exemption use and the specials regime; and the Clinical trials Regulations Medicines for Human Use (Clinical Trials) Regulations 2004 SI 2004 / 1031, regarding good clinical practice in the conduct of clinical trials on medicinal products for human use. For unlicensed use in the UK, manufacture is expected to be performed either under a Manufacturer’s Licence for Exempt Advanced Therapy medicinal Products (MeAT) or in the case of special clinical need under a Manufacturer's Specials licence. In addition, depending on the starting materials and nature of the product, additional specific legislation may need to be considered e.g. The Human Tissue (Quality and Safety for Human Application) Regulations, 2007 (as amended) for the donation, procurement and testing of the human tissue or cells. It is important to ensure that other authorisations and licences are in place, for instance, consideration may need to be given to Health & Safety Executive (HSE) for contained use of Genetically Modified Organisms, Human Fertilisation and Embryology Authority (HFEA) for Embryonic considerations and Department for Rural Affairs (DEFRA) for materials that may include animal pathogens.

To this effect early engagement with regulators is recommended, for example via the MHRA Innovation office at https://www.gov.uk/government/groups/mhra-innovation-office. The Innovation Office and Regulatory Advice Service for Regenerative Medicines (RASRM) advice services offer research and development professionals across academia, industry and the NHS (including clinicians) a single point of access to free, joined-up regulatory information, advice and guidance. Through RASRM, this includes advice from the Health Research Authority (HRA), HFEA, Human Tissue Authority (HTA), and MHRA (Medicines and Healthcare products Regulatory Agency). Where needed, the advice service can also link up to other specialist bodies such as the HSE and DEFRA. Detailed scientific advice can be obtained from the MHRA at https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra. MHRA has a new pathway to support innovative approaches to the safe, timely and efficient development of medicines to improve patient access through the Innovative Licensing and Access Pathway (ILAP) and further details are at https://www.gov.uk/guidance/innovative-licensing-and-access-pathway.

ATMPs are defined in Regulation 2A of the Human Medicines Regulations 2012. In relation to sale or

supply in Great Britain only:

A **gene therapy medicinal product** is a biological medicinal product which has the following characteristics

a. it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and
b. its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

A **somatic cell medicinal product** is a medicinal product which has the following characteristics

a. it contains or consists of cells or tissues that
    i. have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or
    ii. are not intended to be used for the same essential function in the recipient as in the donor; and
b. it is presented as having properties for, or is used in or administered to human beings with a view to, treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

A **tissue engineered product** is a medicinal product which

a. contains or consists of engineered cells or tissues; and
b. is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue.

See Appendix A for further details

Information on ATMPs can be found on the following links:

1. This link directs to the MHRA site for information on how to get a marketing authorisation for a regenerative medicine so it can be sold and supplied in the UK and Europe. https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing
2. This link directs to the MHRA site for information on clinical trials and investigations http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/index.htm
3. This link directs to the MHRA site relating to the human medicines regulations 2012 http://www.legislation.gov.uk/uksi/2012/1916/contents/made

Information relating to the EU.

1. This link opens a pdf of Directive 2004/23/EC of the European parliament and of the council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:EN:PDF
2. This link opens a pdf of 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, and amending directive 2001/83/ec http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF
3. This link opens a pdf of Regulation (EC) no. 1394/2007 of the European parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending directive 2001/83/EC and regulation (EC) no. 726/2004 http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF
4. This link opens a pdf of 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 http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:EN:PDF

5. This link directs to the European Medicines Agency site relating to Advanced Therapy Medicinal Products. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0

Appendix A – Guidance on Definitions, drawn from Regulation 2A of the Human Medicines Regulations 2012

1. In these Regulations, in their application to products for sale or supply in Great Britain only, “advanced therapy medicinal product” means any of the following products

    a. a gene therapy medicinal product;
    b. a somatic cell therapy medicinal product; or
    c. a tissue engineered product.

2. A “gene therapy medicinal product” is a biological medicinal product which has the following characteristics

    a. it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and
    b. its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

3. A vaccine against infectious diseases is not to be treated as a gene therapy medicinal product.

4. A “somatic cell medicinal product” is a medicinal product which has the following characteristics

    a. it contains or consists of cell or tissues that
        i. have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or
        ii. are not intended to be used for the same essential function in the recipient as in the donor; and
    b. it is presented as having properties for, or is used in or administered to human beings with a view to, treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

5. A “tissue engineered product” is a medicinal product which

    a. contains or consists of engineered cells or tissues; and
    b. is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue.

6. A tissue engineered product may contain

    a. cells or tissues of human or animal origin;
    b. viable or non-viable cells or tissues; and

c. additional substances, including cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

7. A product is not a tissue engineered product if it

a. contains or consists exclusively of non-viable human or animal cells or tissues;
b. does not contain any viable cells or tissues; and
c. does not act principally by pharmacological, immunological or metabolic action.

8. Cells or tissues are engineered if they

a. have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved; or
b. are not intended to be used for the same essential function in the recipient as in the donor.

9. The following manipulations are not substantial manipulations for the purposes of paragraphs (4)(a) and (8)(a)

a. cutting;
b. grinding;
c. shaping;
d. centrifugation;
e. soaking in antibiotic or antimicrobial solutions;
f. sterilisation;
g. irradiation;
h. cell separation, concentration or purification;
i. filtering;
j. lyophilisation;
k. freezing;
l. cryopreservation; and
m. vitrification.

10. In these Regulations, in their application to products for sale or supply in Great Britain only, “combined advanced therapy medicinal product” means an advanced therapy medicinal product

a. which incorporates, as an integral part of the product, one or more medical devices or one or more active implantable medical devices; and
b. the cellular part of which
    i. contains viable cells or tissues; or
    ii. contains non-viable cells or tissues which are liable to act upon the human body with action that can be considered as primary to that of the medical devices.

11. Where an advanced therapy medicinal product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues is to be treated as the principal mode of action of the product.

12. An advanced therapy medicinal product containing both autologous and allogeneic cells or tissues is to be treated as being for allogeneic use.

13. A product which falls within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product is to be treated as a tissue engineered product.

14. A product which falls within the definition

    a. a somatic cell therapy medicinal product or a tissue engineered product; and
    b. a gene therapy medicinal product, is to be treated as a gene therapy medicinal product