

Guidelines for the Blood Transfusion and Tissue Transplantation Services in the UK

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Annex 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, or
- a tissue engineered product.

ATMPs are governed by UK medicines legislation and 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.

A6.1. Legislation and regulation

Legislation around ATMPs include:

- The [Human Medicines Regulations 2012](#) (Statutory Instrument [SI] 2012 No. 1916), setting the rules for marketing authorisation and pharmacovigilance, hospital exemption use and the specials regime; and
- The [Medicines for Human Use \(Clinical Trials\) Regulations 2004](#) (SI 2004 No. 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](#) (SI 2007 No. 1523) 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 the Health and Safety Executive (HSE) for contained use of genetically modified organisms, the Human Fertilisation and Embryology Authority (HFEA) for embryonic considerations, and the

Department for Environment, Food and Rural Affairs (Defra) for materials that may include animal pathogens.

To this effect, early engagement with regulators is recommended, for example via the [Medicines and Healthcare products Regulatory Agency \(MHRA\) Innovation Office](#). The Innovation Office and the Regulatory Advice Service for Regenerative Medicines (RASRM) advice services offer research and development professionals across academia, industry and the NHS (including clinicians) with 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), the Human Tissue Authority (HTA), the HFEA and the MHRA. 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 website](#).

The 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 \(ILAP\)](#).

A6.2. Definitions

ATMPs are defined in [Regulation 2A](#) of the Human Medicines Regulations 2012. The full text of Regulation 2A is provided in appendix A below for reference. The following definitions in relation to the sale or supply of ATMPs apply in Great Britain only.

Gene therapy medicinal products

A gene therapy medicinal product is a biological medicinal product which:

1. 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
2. has a therapeutic, prophylactic or diagnostic effect relating directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Somatic cell medicinal products

A somatic cell medicinal product is a medicinal product which:

1. contains or consists of cells or tissues that:
 - a. 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
 - b. are not intended to be used for the same essential function in the recipient as in the donor; and
2. 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.

Tissue engineered products

A tissue engineered product is a medicinal product which:

1. contains or consists of engineered cells or tissues; and
2. 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.

A6.3. Further information

The MHRA website provides guidance on how to get [marketing authorisation](#) for a regenerative medicine so it can be sold and supplied in the UK and Europe and information on [clinical trials and investigations](#).

The following European Union (EU) Directives and Regulations relate to ATMPs:

- [Directive 2004/23/EC](#) of the European parliament and of the council of 31 March 2004, setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
- [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
- [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
- [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 European Medicines Agency (EMA) also provides an [overview of ATMPs](#).

Appendix A

[The Human Medicines Regulation 2012](#) (Statutory Instrument 2012 No. 1916)

PART 1 – General

[2A. Definition of advanced therapy medicinal product etc.](#)

- (1) In these Regulations “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 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.
- (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 “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 of—
- (a) a somatic cell therapy medicinal product or a tissue engineered product; and
 - (b) a gene therapy medicinal product,
 - (c) is to be treated as a gene therapy medicinal product.