

The regulation of advanced therapy medicinal products

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The development of medicine, biomicrobiology and biotechnology has led to the emergence of a relatively new category of **medicinal products** that use gene therapy, somatic cell therapy and engineered tissues for preventing, treating or even curing human diseases. The novelty, complexity and diversity of such products has demanded new regulatory tools to allow an appropriate balancing of the risks and the benefits for the patients. European legislature regulates this category of products as '**advanced therapy medicinal products (ATMPs)**' in order to ensure the highest level of protection of public health and to take into account their specific challenges, in particular with regard to **clinical trials**, manufacturing and **pharmacovigilance**. However, the regulation of the tissues and cells and of genetically modified organisms (GMOs) which are used as starting materials for ATMPs remains national and therefore differs from one Member State to another. Such differences have led to a complex regulatory landscape for ATMP.

This Practice Note explores the definition of an **ATMPs**, the regulation of ATMPs, considers the exceptions to marketing authorisation (MA) requirements for ATMPs and looks at the manufacturing, distribution and import/export of ATMPs under UK law.

What is an advanced therapy medicinal product?

ATMPs are diverse in nature due to the variability of their starting materials. **Regulation (EC) No 1394/2007** (the ATMP Regulation) defines an ATMP as:

'any of the following medicinal products for human use:

- a gene therapy medicinal product as defined in Part IV of Annex I to **Directive 2001/83/EC**
- a somatic cell therapy medicinal product as defined in Part IV of Annex I to **Directive 2001/83/EC**
- a tissue-engineered product as defined in point (b)'

There are therefore three categories of **ATMP** that are based on genes, cells (including stem cells), and tissues, respectively. ATMPs are a type of what is known as regenerative medicine (which refers to methods to replace or regenerate human cells, tissues or organs in order to restore or establish normal function and includes cell therapies, tissue engineering, gene therapy and biomedical engineering as well as more traditional treatments involving pharmaceuticals, biologics and devices).

Each category of **ATMP** is explored in more detail below.

References:

Regulatory Tools for ATMP, Flory and Reinhardt, Transf Med Hemother, 2013 December; 40(6): pp 409–412

References:

Regulation (EC) No 1394/2007

References:

Article 2 of Regulation (EC) No 1394/2007

References:

2013 House of Lords report on Regenerative Medicine

Gene therapy medicinal products

Part IV of Annex I of Directive 2001/83/EC Part IV of Annex I to Directive 2001/83/EC (the Pharmaceutical Code) defines a gene therapy medicinal product as a biological medicinal product which has the following characteristics:

- 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
- 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

Gene therapy medicinal products are highly diverse products. They include therapeutic vaccines (except those against infectious diseases), gene therapy products based on allogenic cells (coming from another human being), xenogeneic cells (coming from a different species—ie non-human animal cells) or autologous human cells (emanating from the patient themselves) and administration of ready-prepared vectors with inserted genetic material.

Somatic cell therapy medicinal products

Part IV of Annex I of the Pharmaceutical Code defines a somatic cell therapy medicinal product as a biological medicinal product which has the following characteristics:

- it contains or consists of cells or tissues that 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 of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor
- 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

For the purposes of the first criterion above, Annex I of the ATMP Regulation lists manipulations that are not considered as substantial manipulations (and therefore would not lead to the classification of ATMP). These include: cutting, grinding, shaping, centrifugation, freezing, filtering, cryopreservation, sterilisation, soaking in antibiotic or antimicrobial solutions, irradiation, cell separation, concentration or purification, vitrification and lyophilisation.

Tissue-engineered products

Article 2 of the ATMP Regulation provides a definition of 'tissue-engineered product'. A tissue-engineered product is a product that:

- contains or consists of engineered cells or tissues, and
- 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

References:

Part IV of Annex I of Directive 2001/83/EC

References:

Regulation (EC) No 1394/2007

References:

Article 2 of Regulation (EC) No 1394/2007

A tissue-engineered product may contain:

- cells or tissues of human and/or animal origin, which may be viable or non-viable. Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, are expressly excluded from the definition of a tissue-engineered product
- additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices

Article 2 also specifies that cells or tissues are considered 'engineered' if they have been subject to substantial manipulation (see above) or are not intended to be used for the same essential function(s) in the recipient as in the donor. Grafts and other human applications of tissues and cells without substantial manipulations are subject to Directive 2004/23/EC (the Tissues and Cells Directive) or Directive 2002/98/EC (the Blood Directive) but not to the ATMP Regulation.

Combined ATMPs

Besides the three categories of **ATMPs**, Article 2 distinguishes so-called 'combined ATMPs'. A combined ATMP is legally defined as an ATMPs that:

- incorporates, as an integral part of the product, one or more **medical devices** or active implantable medical devices; and
- the cellular or tissue part of which contains viable cells or tissues; or is liable to act upon the human body with action that can be considered as primary to that of the devices referred to

In cases where a combined contains a **medical device**, the ATMP Regulation requires that:

- the device complies with **Directive 93/42/EC (the Medical Device Directive)** or, if the device is active implantable, with **Directive 90/385/EEC (the Active Implantable Medical Device Directive)** (collectively the Medical Devices Directives) in order to ensure an appropriate level of quality and safety; and
- the results of the assessment of the (active implantable) **medical device** part by a **Notified body** (see Practice Note: **An introduction to the regulation of medical devices—Conformity assessment and Notified Bodies**) should be recognised by the **European Medicines Agency (EMA)** in the evaluation of the combined ATMP

In other words, the **medicinal product** and the **medical device** have to be assessed separately, rather than the combined ATMP being assessed by the **EMA**.

References:

Article 2(1)(b) of Regulation (EC) No 1394/2007

References:

Annex 1 of Regulation (EC) No 1394/2007

Article 2(c) of Regulation (EC) No 1394/2007

References:

Article 2(1)(d) of Regulation (EC) No 1394/2007

References:

Article 9 of Regulation (EC) No 1394/2007

References:

Directive 93/42/EC (the Medical Device Directive)

Directive 90/385/EEC (the Active Implantable Medical Device Directive)

EMA: Procedural advice on the evaluation of combined advanced therapy and the consultation of Notified Bodies in accordance with Article 9 of Regulation (EC) No 1394/2007, 11 Feb 2011

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