Classification and Regulation of Advanced Therapy Medicinal Products

Advanced therapy medicinal products (ATMPs) represent a group of innovative pharmaceuticals that are increasingly gaining importance. It combines gene therapeutics, somatic cell-based products and tissue-based products. ATMPs are often produced in small batches for personalised therapies only. These therapies are particularly important for severe, untreatable or chronic diseases for which conventional approaches have proven to be inadequate. The manufacturing process of the ATMPs is mostly still in development.

Since the European Directive EC 1394/2007 came into force, ATMPs have been classified as medicinal products and, as such, they must be in line with the EU requirements for medicinal products. While the biopharmaceutical industry has significantly intensified its activities in this field, many of these products are being developed and manufactured at universities, hospitals, and small and medium-sized companies[1]. For the development of ATMPs in other than the biopharmaceutical industry, the respective institutions and facilities as well as the regulatory and supervisory authorities are faced with particular challenges in meeting compliance requirements for GMP and licensing. This is also accelerated by frequently used framework conditions, e.g. the open manipulation of cells and tissues necessary for medical / surgical recovery, or the short lifetimes of the recovered ATMP. To cope with these peculiarities, the European Commission (EMA) and the Committee for Advanced Therapies (CAT) published a special guide for ATMP, adopted at the end of 2017, trying to define the expected GMP standards[2,3].

Since 2008, all ATMPs must be approved via the centralised procedure (CP). This will ensure that they are consistent across the EU in terms of evaluation and approval procedures. This makes it easier for companies to commercialise their products and for patients in different Member States to have access to these products.

ATMPs are complex drugs that are subject to very different assessment criteria than those used in the traditional pharmaceutical area. For example, products with or consisting of genetically modified organisms (GMOs) require an environmental risk assessment in order to assess the risks to humans and the environment.

Classification of ATMPs

An 'advanced therapy medicinal product' means a medicinal product for human use, e.g. a gene therapy medicinal product, a somatic cell therapy medicinal product, a tissue engineered product or a 'Combined ATMP' – containing as an integral part of the product a medical device.

The classification of the four main groups of medicinal products is defined in the reflection paper on classification of advanced therapy medicinal products of the EMA, as outlined in the following paragraphs[4].

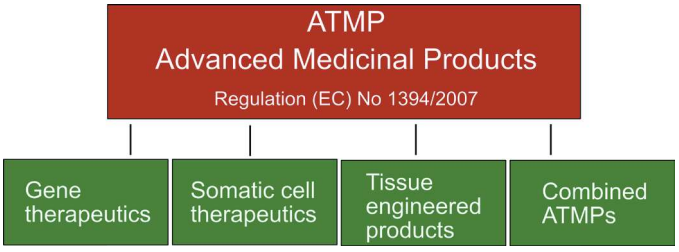

Fig 1. Classification of ATMPs in four main groups (adapted from PEI "www.pei.de").

Gene therapy medicinal product (GTMP) means a biological medicinal product which contains an active substance including 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 shall not include vaccines against infectious diseases.

Somatic cell therapy medicinal product means a biological medicinal product which 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 cells or tissues that are not intended to be used for the same essential function in the recipient and the donor. This product is also 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 product means a product that contains or consists of engineered cells or tissues, and having properties for regenerating, repairing or replacing a human tissue, or is used in or administered to human beings with a view to these properties. A tissue engineered product may contain cells or tissues of human or animal origin. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices. 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 excluded from this definition.

A combined advanced therapy medicinal product means an advanced therapy medicinal product that must incorporate, as an integral part of the product, one or more (implantable) medical devices, and its cellular or tissue part must contain viable cells or tissues, or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

As an illustration, the Committee for Advanced Therapies (CAT) provided two scientific recommendations for classifications for genetically modified T cells encoding an exogenous

thymidine kinase gene[3]. In these cases, it could be classified as ATMP or as GTMP. To decide if a product is an ATMP, Figure 2 shows a flow chart with various questions to serve for orientation.

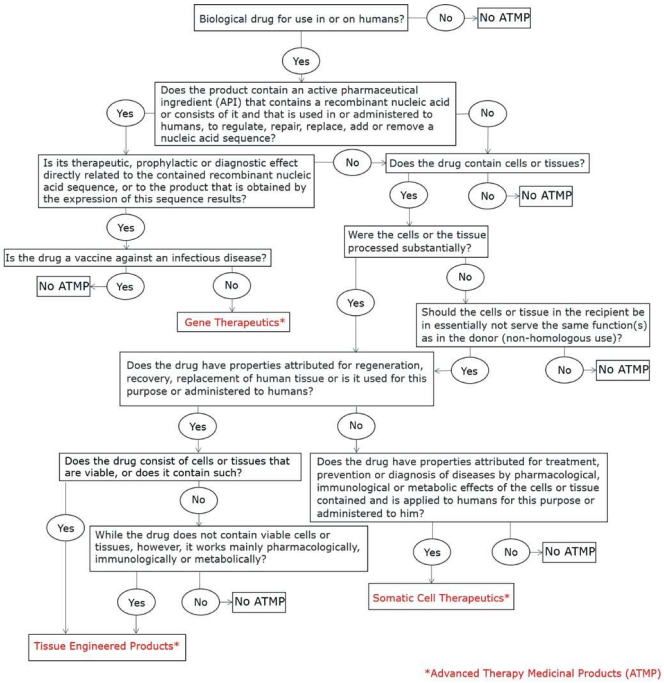

Fig. 2 ATMP decision flow chart (adapted from PEI "www.pei.de")..

Quality Aspects

The 'Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells' defines genetic manipulation as not necessarily having to take place in the human body, since for example products consisting of genetically modified cells generated *ex vivo* have also been classified as a gene therapy medicinal product[5]. The efficiency of genetic modification may depend on target cell features (primary cells or cell lines, adherent or in suspension, dividing or quiescent), features of the cell culture (culture system such as flasks, cell seeding density or concentration) and of course on type and amount of vector. Regarding vector systems for transferring the gene of interest (GOI) into a target cell, a supercoiled minicircle DNA (MC) is an efficient and safe alternative to plasmid DNA. Amongst others, these vectors are classified as starting materials.

Starting materials used for the production of genetically modified cells and genome edited products shall be carefully qualified to assure a consistent manufacturing process. Detailed information should be provided on the manufacturing process, control of materials, characterisation, process development, control of critical steps, process validation, analytical procedures, and stability. Starting materials characterisation and quality control data should be included in the common technical document (CTD) under the heading of "control of materials", either when produced in house or supplied by another manufacturer. The starting material should be stored under controlled and optimal conditions to ensure maintenance of critical characteristics for the intended use and, in particular, to ensure an acceptable level of consistency in product quality, that should be maintained within the parameters of the clinically tested batches.

For transient production of lentivirus (LV), retrovirus (RV), adeno-associated virus (AAV) or other viral vectors from producer cell lines, the sequence of plasmids used to provide vector function(s) should be verified before their use in the transient production. For the production of recombinant mRNA or proteins, the coding sequences of the plasmids used should be verified before their use in the transient production. The use of unrelated DNA sequences, such as selection markers, that can end up in the final genetically-modified cells should be avoided unless justified. Minicircles are also beneficial in this case, because they have no bacterial backbone and therefore neither a bacterial resistance gene and origin of replication nor significant numbers of CpG islands[6].

Conclusion

The EMA guidelines are not intended to limit the development of new technologies. While imposing some additional obligations on ATMP manufacturers, such as defining starting material specifications, they also provide autonomy and flexibility through a risk-based approach to ensure compliance in fast-growing areas.

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