## Original Article

# Exploratory assessment of the current EU regulatory framework for development of advanced therapies

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**ABSTRACT** **The Advanced Therapy Medicinal Products (ATMP) Regulation provides a necessary regulatory framework for the commercialisation and use of regenerative medicine-based therapeutic products in the EU. However, concerns have been raised about the appropriateness of the regulatory strategy it has adopted to address different, complex and evolving categories of medicinal products. This article explores some of the potential shortfalls of the ATMP Regulation with regard to facilitating the research and development of advanced therapies in the present and in the future. It concludes that while providing a much needed harmonised regulatory framework for the companies operating in the sector, the new regulation has yet to demonstrate its capacity to keep up with radical technology changes.**
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## INTRODUCTION

On 26 June 2009 the first marketing authorisation for an advanced therapy medicinal product was granted under the new regulatory regime introduced on 30 December 2008 by the Advanced Therapy Medicinal Products (ATMP) Regulation.[1] The ATMP Regulation attempts to create a centralised marketing authorisation and harmonised regulatory requirements in the European Union (EU) for

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three main categories of products, namely gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (CTMPs) and tissue-engineered products (TEPs). GTMPs and CTMPs encompass products in which genes or cells have been transformed to have a prophylactic, diagnostic or therapeutic effect once transferred into a patient. TEPs involve the growing of living cells, seeded on a supporting structure, to form a three-dimensional tissue or organ to be implanted into a patient to repair or replace tissue damaged by injury, disease or the aging process. This category also includes combined products containing viable human cells and tissues in addition to a medical device.

The ATMP Regulation represents an ambitious attempt to provide a harmonised regulatory framework catering for a large and diverse range of advanced therapies. It has been welcomed by the regenerative medicine industry and is expected to have a positive impact on the availability of innovative treatments to patients across the EU. It should also impact a number of other health-care issues like the length of stay in hospital, the improvement of quality of care and, not the least, the comfort of the patient.

However, questions remain regarding the appropriateness of the 'umbrella' strategy EU regulators have adopted to design the ATMP Regulation, which brings three innovative categories of medicinal products under one regulatory text, as well as the appropriateness of some of the ATMP requirements. Concerns have also been expressed by product developers regarding the capacity of the ATMP Regulation to adapt to further technology evolutions and to the development of innovative and complex applications, combining aspects of cell-based and gene-based therapies.

This article explores some of the potential shortfalls that the ATMP Regulation presents with regard to facilitating the research and development of advanced therapies in the present and in the future. It deals with the different therapies covered by the ATMP Regulation, that is GTMPs, CTMPs and TEPs, and provides an overview of a number of issues including the design of clinical trials and the bio-safety of GTMPs, the characterisation requirements regarding CTMPs and the assessment procedure for tissue-engineered products.

## GENE THERAPY MEDICINAL PRODUCTS

As noted above, GTMPs are products where genes have been transformed to have a prophylactic, diagnostic or therapeutic effect once transferred into a patient. The current structure of the ATMP Regulation raises three key issues for the development of these products, which are their cost of development, the design of their clinical trials and the expertise needed to assess them.

Many large companies developing gene therapy products have exited because of the setbacks the field has experienced as well as stringent regulatory requirements. This has led to a situation wherein the public research institutions such as universities are at the forefront of research and development. The increased cost of maintaining good manufacturing practice and good laboratory practice, as well as the increasing cost associated with getting approval and conducting clinical trials, may act as an inhibitor on public research funding bodies.

The increasing cost, for example the accredited synthesis of a batch of viral vector could cost around £500 000 in the United Kingdom, puts significant pressures on academic and public funding bodies. These high and potentially prohibitive costs in the United Kingdom may not be present in the United States, where the Food and Drug Administration has the discretion not to demand some procedures and assays when there is a consensus that there are no imminent safety issues.

Conducting clinical trials for GTMPs remains an issue under the ATMP Regulation. The Regulation does not challenge the

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requirements set by the EU Directive on clinical trials[2] even though those requirements are generally considered stringent by gene therapy developers.[3] In addition, as the Directive leaves some discretionary powers to Member States to develop detailed procedures, it may lead to a number of discrepancies and to an uneven growth of this field across the EU. For instance, plasmid DNA is considered as a genetically modified organism in France but not in other countries such as Germany.[4] In the case of multi-centre gene therapy trials, across two or more EU Member States whose definitions of genetically modified organisms differ, this could result in increased complexity of the clinical trials process. In addition, the period of 210 days needed by the European Medicine Agency and its relevant subcommittee to assess the dossier of a GTMP before granting a potential marketing authorisation is considered too lengthy by many workers/product developers.[5]

Another issue lies in the varied expertise and talent pool that exists across the EU regulatory bodies that have the remit to evaluate gene therapy trials. Such trials may therefore be subjected to a heterogeneous mix of evaluation and standard regimes depending on where in the 27 Member States of the EU the trial takes place. Information sharing between researchers and regulators also varies greatly between the western EU states and the new member entrants, as does the adoption of standards related to consent provision and bio-safety of GTMPs. It should also be kept in mind that some GTMPs, for instance for the treatment of cancer, are likely to be more effective as adjuvants in combination with conventional therapies. In this case, assessing the efficacy of a GTMP will demand a new approach to clinical trial design.[6]

A stock-taking report on the ATMP Regulation is being planned by the EU Commission for December 2012. It is meant to assess if the new regulation can keep pace with technology changes, including issues such as the bio-safety of newly designed vectors and delivery systems, the use of new technologies and strategies such as antisense and RNA interference, enzyme-pro-drug activation, oncolytic virus therapy and nano-technology among others. The 2012 stock-taking report will discuss and may address some of these issues but this intervening period of several years may act as a deterrent for some gene therapy developers.

## SOMATIC CELL THERAPY MEDICINAL PRODUCTS

There are three limitations with the ATMP in comparison with the evolving state of somatic CTMPs. They include standards for risk management, clear Good Manufacturing Practice (GMP) requirements and coordination in clinical trials.

Although the ATMP Regulation looks to establish integrated and harmonised procedures for product development, specific standards for measuring the risks and benefits of different stem cell populations mostly remain ill-defined. This is of particular concern for CTMPs, as stem cell bio-processing for a therapeutic application involves a variety of approaches, which necessitate the implementation of clear and tailored characterisation requirements. For instance, multi-potent cells may be transplanted that give rise to terminally differentiated cells *in vivo*. Alternatively, cells may be allowed to differentiate fully in culture before being transplanted or in other cases a mixture of both multi-potent and differentiated cells may be transplanted.[7]

Therefore, tailored characterisation standards involving multi-parametric analytical tests and definition of suitable animal models are required for preclinical safety testing of these cell-based therapeutics. Typical safety tests range from morphological evaluation, detection of phenotype-specific cell surface markers, gene and protein expression analysis, cellular impurities profile assessment, biological assays for potency and MHC/HLA expression to predict immunologic compatibility. Further, standardisation of preclinical safety tests and of chemistry, manufacturing and controls (CMC)

is the key to ensure consistent measurement of safety and quality of these products. Short shelf-life and the use of autologous products restrict their end-stage testing that further necessitates implementation of alternative exemptions and appropriate standards.

Addressing CMC-related product and process characterisation issues, starting from early stages of raw material control, is therefore critical for manufacturing stem cell-based therapies. The presence of undifferentiated or partially differentiated cells in the final cellular therapeutic could result in adverse reactions such as teratoma or adventitious tissue formation, genomic or epigenetic modifications, immunological reactions or transmission of infections.[8,9] In most cases the presence of these 'undesirable' cells in the final cell product can affect product potency.[4] Therapies involving a mixture of cell types in the final cellular product further add to the complexity of setting purity standards.

GMP requirements represent another source of concern for developers of CTMPs, as some of them are still in the process of being finalised.[10] The general process risks can be mitigated by following a set of GMP guidelines that add to the safety as well as potency of the final product. A major source of concern lies in the fact that the engineered stem cells would come under the regime designed for CTMPs, which have certain pharmaceutical-like characteristics but are unlikely to have large-scale classic randomised, double-blinded clinical trials nor will be mass produced as conventional pharma products. Therefore, the associated technical requirements will need to be documented with appropriate scope for technical innovation and product evolution.

The lack of a coordinated centralised system and differential application for clinical trials across EU is considered as much a barrier for stem CTMP developer as it is for GTMPs. Having to approach each member state and adhere to their individual clinical trial requirements with varying concerns and expectations places significant pressure on Small and Medium Enterprises, who often only take a product to early clinical development owing to their limited resources and infrastructure. Coordination is needed to achieve safe clinical trial mandates, for instance stoppage of treatment on adverse event occurrence and *in vivo* cellular imaging to further provide solidity to the overall product safety.

Manufacturing innovative therapeutics and carrying out clinical trials are dispersing around the world as a result of globalisation. In such a context, the EU Commission needs to influence the offshore manufacture of products that might reach the EU market ultimately and ensures that adequate import controls are in place. For this, local presence or liaison with local regulatory authorities will be helpful for effectively auditing the manufacturing sites. The larger pools of potential study subjects and lower costs attract trial sponsors to other countries. Monitoring the early phase data from such trials with the cultural differences of subjects and regional disparity would also be aided by local presence or linkages. Tailored European guidelines on appropriate trial design, patient follow-up, auditing manufacturing facilities, especially overseas, and assessing trial data from cohorts that may be non-representative would assist developers in navigating the regulatory framework.

## TISSUE-ENGINEERED PRODUCTS

The current version of the ATMP Regulation raises a number of issues for TEPs with regard to their assessment when they combine cells and a device part and to the criterion used for their classification.

The ATMP Regulation's definition for TEPs encapsulates products containing engineered cells or tissues and which may also incorporate a device component in addition to their cellular or tissue part. Such TEPs are called 'combined products' and their assessment raises a specific set of issues as they present

characteristics of both medicinal products and medical devices.[11] In order to assess combined products, the ATMP Regulation provides for a differentiated approach depending on whether an assessment of the medical device part has, or has not, already been made by a notified body. A notified body is a body designated by the competent authority of a member state, the Medicines and Healthcare products Regulatory Agency in the case of the United Kingdom, to carry out a compliance assessment of medium and high-risk devices. An application for marketing authorisation of a TEP that contains a medical device has to present evidence that the device complies with the requirements laid down by the Medical Device Directives and such evidence is usually based on an assessment carried out by a notified body.[12,13] However, some applications do not include any assessment from a notified body and, in this case, the European Medicines Agency (EMA), which is responsible for granting licences, may, or may not, commission a notified body to assess the medical device part.

This optional consultation process within the ATMP Regulation for assessing medical devices and its consequent relegation of notified bodies has been questioned by a number of stakeholders. First, rendering the consultation of a notified body possible but not compulsory requires that the expertise needed to assess the medical device part of a combination product is sufficiently represented within the EMA and more specifically within a newly created committee embedded within the EMA and named Committee for Advanced Therapies. Second, the expertise gained by notified bodies in assessing complex medical device may prove useful in the case of next-generation combined products. Third, in a context of restrained economic resources and rising health-care costs, the targeted integration of notified bodies in the authorisation procedure could help prevent duplication of structures and of expertise. However, these different issues are overlooked by the ATMP Regulation.

The ATMP Regulation addresses the current stage of TEP development, but tissue engineering is a nascent and fast-moving field that is likely to lead to more complex and more sophisticated therapeutic products in the future. Future generations of TEPs are likely to raise a number of convergence and combination issues with, for instance, the integration of human cell therapy with gene-based methods, biomaterials and molecular medicines.[7]

There is a concern that the principal mode of action (PMOA) criterion that EU regulators have adopted to underpin the EU assessment process for TEPs may become inappropriate at that time. Defined as the mode of action that provides the most important therapeutic action of the product, the PMOA criterion is the basis for classifying a combined product under the ATMP regime, if it delivers its PMOA through pharmalogical, immunological or metabolic means, or under the Medical Devices Directive regime, if it delivers its PMOA through mechanic means. Further, with a view to simplifying the assessment process, EU regulators have introduced into the ATMP Regulation a provision stipulating that a combined product containing viable cells will automatically be considered having a principal pharmalogical, immunological or metabolic mode of action and will therefore fall under the scope of this regulation. While such a provision may help address the current state of tissue-engineered products, it may prove problematic to accommodate their technology evolution. There will be a risk that the PMOA criteria will become difficult to define in the case of combined products that can have several and equally important therapeutic effects.

## CONCLUSION

The ATMP Regulation provides a necessary regulatory framework for advanced therapies, but some of its requirements need further refinement to take account of the specificities of the different categories of products it covers. The prescriptive regulatory approach it has adopted may constrain its ability to keep

up with radical technology changes like convergence/combination issues, together with associated characterisation issues, that are likely to be raised by emerging complex innovative medicinal products combining cells, genes, supporting structures and delivery devices. It remains to be seen if the ATMP Regulation will provide in the future the degree of certainty, predictability and flexibility expected by manufacturers and other stakeholders. Engaging with regulators throughout the life cycle of the product is more important than ever for developers, as it will inform the adaptation of the ATMP regulatory framework to technology changes and facilitates transparency in the overall regulatory oversight for regenerative medicine products in the EU.

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