Original Article

ATMP in practice: Towards a new industry landscape in tissue engineering

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ABSTRACT **Regulatory divergences and market fragmentation across member states have hampered the development of the tissue engineering industry in the EU. Addressing this situation by providing a harmonised and more predictable regulatory regime, the regulation on advanced therapy medicinal products (ATMPs) is based on a regulatory strategy that aims to consolidate the increased activity in the domain of regenerative medicine while maintaining the pace of technical development and innovation in this area. The regime draws together the professional expectations of ATMP developers by aiming for a harmonised market access and for providing legal certainty for all stakeholders and concurrently assuring safety and quality of these products to render highest standard of health protection to patients. Still a work in progress as its technical guidelines are in drafting and as it will only apply from December 2008, the ATMP Regulation, which comprises several small and medium sized enterprises (SMEs) friendly provisions, is nevertheless anticipated to have significant impacts on developers. This paper considers some of them.**

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INTRODUCTION

The Regulation (EC) No 1394/2007 defined for advanced therapy medicinal products (ATMPs) merges gene and somatic cell therapies, for which EU regulatory requirements already exist, with tissue-engineered products (TEPs), which so far did not fall under the scope of a defined set of regulations at the EU level.[1]

Responding to industry concerns, the regulation aims to put an end at the existing patchy regulatory situation. In the absence of a comprehensive EU regulatory framework, member states have developed their own set of rules which have resulted in market

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Table 1: Timeline

July 2002	Public consultation launched by the DG Enterprise of the EU Commission to assess the need for a community legal framework on TEPs. Contributions from SMEs represent 55 per cent of the overall contributions
2004	Public consultation launched by DG Enterprise on the content of a future regulatory framework for TEPs
16th April, 2004	Stakeholders' conference organised by the EU Commission
2005	Public consultation launched by DG Enterprise on a draft proposal for a regulation on advanced therapies
16th November, 2005	Publication of the proposed ATMP Regulation by the EU Commission
13th September, 2006	Rejection of the parliamentary report issued by the given committee on the ground that it contains ethical amendments
30th January, 2007	Adoption of the parliamentary report with no ethical amendments
25th April, 2007	Vote on the ATMP Regulation by the European Parliament
31st May, 2007	Agreement on the ATMP Regulation by the EU Council of Ministers
30th October, 2007	Formal adoption of the ATMP Regulation by the EU Council of Ministers
10th December, 2007	Publication of the ATMP Regulation in the *EU Official Journal*
30th December, 2007	Entry into force of the ATMP Regulation
30th December, 2008	Application of the ATMP Regulation to all economic operators

fragmentation.[2] Manufacturers were confused about the 'optimal path' to develop and commercialise TEPs.[3] This problematic assignment of products to the legislation, variable approaches taken by EU member states and a fragmented market introduced a number of issues for the developers from production, application, and post-market follow up (of the products). In this context, the ATMP Regulation is designed by the EU Commission to set up a centralised marketing procedure and to achieve access of TEPs to the whole community market while increasing trust of the user groups in these new products. It will apply from December 2008 and will impart clarity to manufacturers in terms of the requirements of conforming to regulations set for a particular product and the overarching guidelines laid for medicinal products. In parallel, the common and transparent framework will minimise risks and uncertainties faced by the manufacturers. It is therefore anticipated to have a positive impact on the availability of TEPs to patients.[4]

The framework adopted by the ATMP Regulation is a cohesive document built on the directives laid down for medicinal products (gene therapy and somatic cell therapy) for human use (Directive 2001/83/EC), quality and safety standards in respect of human tissues and cells (Directive 2004/23/EC), medical devices (Directive 93/42/EEC), active implantable medical devices (Directive 90/385/EEC), and centralised procedures (Regulation No 726/2004). A timeline of defining milestones in the process of drafting ATMP Regulation since the early 2000s and the participation of industry/developers are shown in Table 1.

THE TWO-STAGED STRATEGY ADOPTED BY EU REGULATORS

Tissue engineering being an emerging and fast-moving field whose technological development and potential risks are not fully foreseeable, EU regulators had to strike a difficult balance between the possibility for patients to gain rapid access to promising therapies and 'appropriate guarantees on safety and quality'.[5] Designing such guarantees was especially tricky as they need to allow for a certain degree of flexibility in order to keep pace with the technological evolution.

EU regulators therefore opted for a two-staged regulatory strategy with a regulatory level built on existing and newly introduced EU provisions, the latter being laid down in priority to deal with TEP marketing authorisation procedure, and a technical level, encompassing all the technical requirements covering the whole development process,

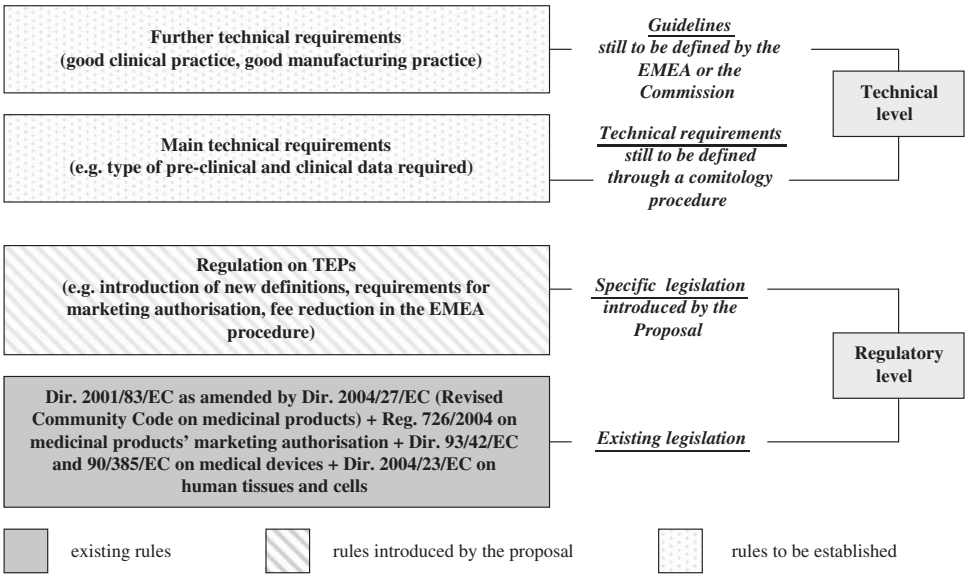

Figure 1: EU Commission regulatory strategy towards TEPs

from production, handling, storage, transport up to traceability of the donor. The overarching framework was therefore limited to fundamental issues, like the centralised marketing procedure and the introduction of specific incentives for small and medium sized enterprises (SMEs), but when it came to good manufacturing practice (GMP) and good clinical practice (GCP), for instance, detailed rules were left in blank. This way, the ATMP Regulation was quicker to draft and adequate flexibility was introduced into the regulation to keep pace with scientific developments.

The combination of a general framework for all ATMPs with flexible provisions, to be drafted by the European Agency for the Evaluation of Medicinal Products (EMEA) or through an EU specific procedure named Comitology that involves the Commission, the European Parliament and member states' representatives, is a determining characteristic of the ATMP Regulation. It explains the complexity of the resulting regulatory structure proposed by the EU Commission which combines numerous pieces of existing legislation with new provisions and to be defined rules (see Figure 1).

A WORK STILL IN PROGRESS

As a consequence of the regulatory strategy the EU Commission opted for, key technical requirements and guidelines for TEPs, entailing important implications for industry, are still in the process of being drafted. Comparing the ATMP Regulation to an 'empty shell', however, does not seem accurate.[6] The regulation is far from being content free although it is true that numerous requirements, upon which depends the practicability of the new regulatory regime, are not yet set with certainty (see Table 2).

Guidelines on GCP, GMP, and traceability are now to be finalised by the Commission, and the EMEA is currently tasked with developing guidelines on post-authorisation risk management. A considerable amount of detailed work before implementation is therefore still required.[7]

Even though the ongoing drafting of the technical requirements makes it difficult to foresee exactly all the possible impacts the ATMP Regulation will have on developers, some hypotheses may nevertheless be advanced.

Table 2: Requirements to be developed subsequent to adoption of the ATMP Regulation

	ATMP requirements still in preparation	*Procedure foreseen by the ATMP Regulation*
Article 4	Good Clinical Practice specific to TEPs	Drawing up of guidelines by the Commission after consulting the EMEA
Article 5	Good Manufacturing Practice specific to TEPs	Drawing up of guidelines by the Commission after consulting the EMEA
Article 8	Evaluation procedure by CAT/CHMP	Drawing up of procedures by the EMEA
Article 14	Post-authorization follow-up of efficacy and adverse reactions+risk management	Drawing up of guidelines by the EMEA
Article 15	Traceability	Drawing up of guidelines by the Commission
Article 18	Scientific evaluation and certification of SME data	Drawing up of requirements by the Commission through the Comitology procedure
Article 24	Adaptation (of annexes) to scientific and technical evolution	Drawing up of requirements by the Commission through the Comitology procedure after consulting the EMEA

DEVELOPMENT OF A PLATFORM PRODUCT

The harmonised access and free movement of ATMPs will render effective operation of this sector assisting their internal market and commercialisation in the EU. By including in its scope gene therapy, somatic cell therapy and TEPs intended for human use, the ATMP Regulation will be useful for SMEs as they generally use their resources in the manufacture of more than one product to keep their options open in terms of market success. The ATMP Regulation does not require them to distinguish between product categories upfront thereby conferring them freedom of activity. The highly complex and innovative manufacturing processes involved can therefore be applied to generate a safe, efficacious, and commercially viable platform product with a broad range of applications under the overall field of regenerative medicine.

COST-COMPLIANCE ISSUE

Under the ATMP Regulation, TEPs will have to comply with the span of regulation established for medicinal products which encompasses a lengthy and costly approval procedure. This could lead to delays in TEPs reaching the market and, compromises the financial survival of small-scale operators.

The manufacturing prerequisites and demands set forth by the centralised marketing authorisation for products with high standards of safety, quality, and efficacy, along with post-authorisation vigilance, will increase the overall cost and duration of incurring market approval. Further, to comply with these new standards, experts identify that some of the research-based technology-intensive SMEs involved in this industry will need major procedural alterations and/or modifications to their products and processes. The magnitude of cost increase will hinge upon the individual position of the manufacturing business on the product cycle and individual regulatory specifications and enactment of the member state. The considerable increase in the size of the accessible market for a specific product may ameliorate some of the cost impacts.

Also, the authorised TEPs will have immediate access to all individual national markets in EU which will foster competition. A single unified market will intensify competition between manufacturers as they strive for increased sales to make up for higher compliance costs to meet the ATMP provisions. New innovative breakthrough technologies formulated by a manufacturer might further raise the bar of regulatory requirements across the EU for their rivals. To cut down costs associated with adaptation and compliance with the ATMP Regulation, and vigilant post-authorisation surveillance practice, larger firms may attempt acquisitions, process outsourcing, or product licensing to capable SMEs. The big businesses will be able to cater to the needs of the European community market more uniformly and

efficaciously, which will lead to market integration on a wider scale.

WHAT DEVELOPERS COULD MAKE THE MOST OF …

Placing TEPs under the EU pharmaceutical regime, the ATMP Regulation entitles TEP manufacturers to benefit from a range of advantages granted to medicinal products, for instance, 'orphan status', conditional marketing authorisation, and compassionate use.[8] These special conditions are of considerable interest for TEP developers as some of them are likely to address unmet clinical needs. The tissue engineering industry is characterised by small biotechnology companies for which a shorter time to market could be crucial for their continued existence as financially viable enterprises.

The free certification of quality and of non-clinical data for SMEs provided by Article 18 of the ATMP Regulation could also positively impact on the industry landscape. This provision allows SMEs to reach the stage at which they have established a proof of principle and assist them to raise funding to engage in clinical trials. The certification granted by the EMEA will help them to convince financial institutions to lend them the required funds or to make a deal with a larger business. The question remains as to whether the regulator has the capacity to deliver the volume of certification that could be required.

The ATMP Regulation also provides for economic incentives like a 90 per cent reduction of fees for scientific advice (eg on the design and conduct of pharmacovigilance and of risk management) and the possibility to defer the payment of fees until the marketing authorisation is granted. In addition, the fee payable by a SME for a marketing authorisation can be reduced by 50 per cent if the applicant can prove that the product represents a particular public health interest in the EU. At last, if a marketing authorisation is not granted, the applicant will not have to pay any fees.

LEVELLING THE PLAYING FIELD?

The ATMP Regulation excludes custom-made TEPs manufactured non-routinely and applied in the same member state in a hospital complying with an individual medical prescription for a patient under the exclusive responsibility of a medical practitioner. This provision, known as the 'hospital exemption', has raised some concerns among SMEs as it could lead to a situation of unfair competition between companies and hospitals. A further concern lies in the definition of hospital which varies from one member state to another and which could result in other regulatory divergences across the EU. But the manufacturing, quality and pharmacovigilance standards, and ethical guidelines to be followed in the manufacture of these products will have to be at par with specific quality standards with coherent national traceability and risk management system as foreseen by the EU Regulation, similar to provisions for commercial developers.

This will provide freedom of activity to clinicians and promote innovation as each treatment will be assessed on its merit. Also, the impact on research-driven hospitals would be minimal, as preclinical and clinical research is exempted from market authorisations for TEPs. But, this freedom might create room for error as producers may get biased and deviate from standard protocol to offset production costs, or due to their unfamiliarity with the stringent testing and validation procedures undertaken by their commercial counterparts. For this, local national authorities will have to be more vigilant so that applicable community principles consociated to quality and safety standards are not subverted. Such treatments with the promise of ultimately becoming a product, if worthy, can be singled out on the basis of merit and commercialisation prospects, and floated in the market in accordance with the relevant regulatory requirements.[9]

Another challenge to the level playing field pursued by the ATMP Regulation lies in the

subsidiary principle that EU regulators have observed and which excludes from the scope of the new regulation any ethical decisions on the acceptance and use of certain cell types, like human embryonic stem cells, and cells derived from those cells. As a result, each member state is entitled to forbid the use of certain cell types and therapies on its territory for ethical reasons. Consequently, some developers may find it impossible to commercialise their product in some member states even though it has been granted a centralised marketing authorisation.

PROMOTION OF PUBLIC CONFIDENCE

TEPs may present risks for human health due to the complex constituents and procedures required in their manufacture and extended implantation *in vivo*. The ATMP framework which demands for rigorous attention to rules and procedures will help in building up the confidence of end-users (patients and clinicians) towards these products, which will eventually contribute to more rapid development of their market as a whole. Harmonised requirements to conduct safety and efficacy analysis and to review clinical studies before placing TEPs in the market are also expected to prevent undue risks as much as possible. In addition, the setting up of a post-marketing vigilance and the comprehensive reporting of adverse events are also expected to trigger a virtuous circle, resulting in increased patient safety and improved quality of life which will further boost the credibility of these products in the minds of the user groups.

Moreover, the non-subjective segmentation of traceability obligations between the marketing authorisation holder (TEP developer) and the hospital, institution, or private practice where the product is used that the ATMP Regulation provides for will assist in detailed follow up of the product's efficacy, safety, and adverse reactions, if any, and will contribute to foster public confidence. The obligation of the developer begins from sourcing of raw materials and ends at delivery to the end user. Further patient and product traceability comes under the purview of the establishment where the product is used. This will help in associating each product to the recipient, and in addition maintaining and protecting the exclusive physician–patient confidentiality.

A HELPFUL POOLING OF EXPERTISE

The setting up within the EMEA of a special committee, the Committee for Advanced Therapies (CAT), to work with already existing working parties (BWP, GTWP, CPWP), echoes the complex nature of TEPs as well as the expertise required by a regulatory body to endorse such products. Tasked with drafting opinion on the quality, safety, and efficacy of a specific ATMP, the CAT will offer not only recommendations to the Committee for Medicinal Products for Human Use (CHMP), responsible for issuing the final scientific opinion, but also scientific expertise and protocol assistance to the developers. TEP developers have welcomed the creation of the CAT as TEP assessment asks for very specific expertise but they have also voiced some concerns. The CAT's demand for suitably qualified members might result in shortages as not many national agencies have experience in this emerging science, and competition for personnel from other-related fields like pharmaceutical or medical devices will add further pressure. Possible conflicts of interest may further complicate the task of populating the new committee.

DEVELOPERS/REGULATORS: A NEW PARTNERSHIP

It is through use that regulations get revised and refined. Developers need therefore to work together with regulators to ensure that the new regulation in place for TEPs is practicable. For instance, the facilitation CAT will operate to exchange information and ideas along with providing in-depth knowledge

on navigating through the unique regulatory processes, which represents an interesting route for communication and strategic approaches between regulators and developers.

Regarding reimbursement, a dominant issue when it comes to developing commercially viable TEPs, it is suggested that developers commence the reimbursement process during the inception phase of product development or latest before commencing phased clinical trials due to the current lack of precedence and compensation determinants.

For successful generation of ATMP-based innovative therapies, developers will also have to discuss with regulators the way to adopt a conciliatory approach towards the statistically significant efficacy testing of these therapies through conventional approaches. Classic randomised, double-blinded clinical trials will not be possible, for instance, where invasive procedures using autologous substances will be involved.

Further to help their cause, TEP developers should regard regulators as a potential customer from the very inception stage of their product manufacture and thus should incorporate the EU community level regulatory protocol within their product manufacturing lifecycle and clinical testing protocols from the beginning. This will help them comply with the demands laid down in the new regulation and prevent late stage process changes when the product is positioned for approval.

CONCLUSION

The importance of standardising regulations for TEP developers has become increasingly obvious seeing the ongoing conundrums in the development of these products and the market fragmentation for their trading. Manufacturers agree that normalisation through regulatory standards is imperative across the field. The pressure on the developers to meet heightened regulatory compliance may lead some to bankruptcy but will also move others towards product development with ultimately lower clinical and business risk as well as attractive to investors. In the long run, the hope is that the regulatory framework set up by the ATMP Regulation will not only direct but also cater to the growth and development of innovative-research technology-intensive SMEs.

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REFERENCES AND NOTES

1. Williams, D. (2007). A European regulatory pathway for tissue engineering – at last. *Med. Device Technol.* **18**(5), 8.
2. Brevignon Dodin, L. and Livesey, F. (2006). Regulation of tissue engineered products in the European union: Where are we heading? *Regenerative Med.* **1**(5), 709–714.
3. Sanzenbacher, R., Dwenger, A., Schuessler-Lenz, M., Cichutek, K. and Flory, E. (2007). European regulation tackles tissue engineering. *Nat. Biotechnol.* **25**(10), 1089–1091.
4. Kent, J., Faulkner, A., Geesink, I. and Fitzpatrick, D. (2006). Towards governance of human tissue engineered technologies in Europe: Framing the case for a new regulatory regime. *Technol. Forecast. Soc. Changes* **73**, 41–60.
5. Enterprise Directorate-General (2002). *Consultation Document on the Need for a Legislative Framework for Human Tissue Engineering and Tissue Engineered Products*, EU Commission, Brussels.
6. Dupraz-Poiseau, A., Le Goualher, E. and Mudge, S. (2006). Insights into the new proposed EU regulation on advanced therapy medicinal products. *Regul. Rapporteur* **3**(3), 2–4.
7. Pickering, G. (2007). The new advanced therapies regulation: Levelling the playing field for innovation, http://www.euralex.co.uk (accessed 23rd January, 2008).
8. Hughes-Wilson, W. & Mackay, D. (2007). European approval system for advanced therapies: Good news for patients and innovators alike. *Regenerative Med.* **2**(1), 5–6.
9. This is not the intent of the regulation.