

The Regulation of Advanced Therapies: Perspectives from the EU

The new regulation on advanced therapy products has closed a gap in the EU regulatory framework, but how will it serve industry compared with the older system in the US? *Wolfgang Rehmann and Gareth Morgan* report.

This article compares and contrasts the regulatory frameworks in the US and the European Union for so-called "advanced therapies" that are being developed from human blood, cells, skin, bone and tissues. Such therapies are revolutionising the treatment of diseases and injuries, such as cancer, Parkinson's disease, burns and cartilage injuries and regulating them is an important issue for governments.

In the US, the regulatory scheme for advanced therapies initially was limited to human blood and basic tissues, such as bone, skin, ligaments, tendons and others intended for homologous use. In 2005, the Food and Drug Administration amended its regulatory framework by adding a number of components dealing with the eligibility of donors of human cells, good tissue practices, testing, labelling and other important requirements for guaranteeing product safety. The FDA not only requires compliance with the relevant standards, which are constantly evolving and set out in guidelines, but also insists that products receive authorisation before their marketing as a drug, biological or medical device. The extensive federal control is based on the FDA's use of Section 361 of the Public Health Service Act on prevention of communicable disease transmission¹ and, unlike in the EU, is not based on a new regulatory framework implemented specifically for advanced therapy medicinal products.

This new European legal framework – Regulation (EC) No 1394/2007 – was implemented on 30 December 2008 and is applicable for new products coming on to the market². Prior to the regulation, products derived from genes and cells were mostly classified as pharmaceuticals; tissue-engineered products were not explicitly covered by the existing legal framework and were thus only partly classified as pharmaceuticals or as medical devices. Also, regulations were not harmonised across EU member states.

Objectives and scope

The new EU regulation completes the framework on advanced therapies, which had already contained rules and regulations setting standards for the donation, procurement, testing, processing, storage and distribution of human tissues and cells³. The new regulation applies to ATMPs over and above the requirements of the European regulatory regime for human medicines set out in Directive 2001/83/EC (as amended)⁴. Therefore, it should be remembered that the regime outlined below is additional and complementary to those regulatory requirements already set out for "mainstream" medicinal products.

The main elements of the legal framework established by the new regulation are: a centralised market authorisation procedure; the creation of a new expert committee, the Committee for Advanced Therapies, within the European Medicines Agency to assess ATMPs; new, tailor-made technical requirements for the products at stake; risk management and traceability requirements; and special incentives for small- and medium-sized enterprises to stimulate technological entrepreneurship.

By 1997, the FDA had already outlined five areas of regulatory concern regarding therapies derived from human tissues and cells, namely preventing transmission of communicable disease, safe processing and handling, clinical safety and effectiveness, promotional claims and monitoring of industry. Subsequently, the FDA developed a regulatory system for the oversight of these products and brought together the relevant concepts and regulatory principles under the overarching principle of good tissue practice. While it has undergone significant evolution, the FDA's model does not encompass the increasingly broad nature of advanced therapies under one comprehensive regulatory scheme. It is this regulatory framework that the new EU regulation intends to establish.

Both the European and US regulatory schemes at first focused on human blood and basic tissues intended for homologous use. However, the new EU regulation, together with preceding directives, now provides for an overall legal framework for commercial ATMPs. It covers the three groups of products: gene therapy products; somatic cell therapy products; and tissue-engineered products.

By clearly defining these three groups of products, the European regulation aims to correct past uncertainty regarding what constitutes an advanced therapy for the purpose of establishing the scope and applicability of regulations. It also provides clarity for the oversight agencies, regulators, academics and companies that work in this area. Previously, each stakeholder group had its own way of classifying what was and what was not considered to be an advanced therapy. The regulation also

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...by covering the three main groups of ATMPs

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The regulation's clear definitions also establish what it does not cover

provides one framework for the manufacture and marketing of advanced therapies, as well as issues related to approvals, labelling, monitoring and risk management. The clear definitions also establish what is not covered by the regulation. This includes ATMPs produced in a clinic for one-time use by a doctor for a single patient. Products harvested from a patient for use only in that patient are also exempt. In the case of hospitals producing ATMPs for wider use, they would be treated under the regulation as any company producing or marketing advanced therapies.

Clinical development

The central objective of the new EU regulation is to create a single, harmonised framework for approving ATMPs. This ensures universal standards of safety, quality and efficacy on the one hand and access to the whole European market on the other. The regulation also creates specific rules for ATMPs regarding the evaluation of their efficacy and therapeutic claims. When an ATMP enters clinical development, the same requirements used for other pharmaceuticals apply, but additional requirements have to be met regarding the specifics of ATMPs.

ATMP clinical development plans should include pharmacodynamic studies, pharmacokinetic studies, mechanism of action studies, dose-finding studies and randomised clinical trials as required for other medicinal products. But because of specific biologic characteristics of the ATMP, alternative approaches to Phase I and II clinical trials may be required and these must be justified on a case-by-case basis. The EMEA has produced a guideline on human cell-based medicinal products that came into effect on 1 September 2008⁵. This document contains general guidance relating to quality and manufacturing, nonclinical and clinical data that will be required in order to assemble a dossier for the approval of an ATMP. It replaces the guidance document entitled Points to Consider on the Manufacturing and Quality Control of Human Somatic Cell Therapy Medicinal Products⁶. Other documents address risk management issues unique to other types of ATMPs and applicants should ensure that they address the latest guidance when preparing their risk management plans.

This regulatory approach is (or has the potential to be) in marked contrast to the situation in the US. There, the FDA has very much adopted a case-by-case analysis of ATMPs with little product "class" guidance to instruct compliance. The relevant department of the FDA that deals with ATMPs is the Center for Biologics Evaluation and Research and, within this section, the Office of Cellular, Tissue and Gene Therapies. This office will typically arrange a pre-IND (investigational new drug) meeting with prospective applicants and agree a specific protocol, which will eventually lead to a biologics licence application for approval of the product.

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Although this sounds straightforward, recent history has demonstrated that the data required in order to complete a BLA to the requisite standard could cause problems for ATMPs. Contained within the BLA is a section that requires the applicant to demonstrate that the production process for the ATMP is sufficiently controlled as regards characterisation and quality. Clearly ATMPs that involve modifying a patient's own cells have a variable content that makes compliance with the above FDA requirement difficult. Most notably, Dendreon, with its prostate cancer vaccine product Provenge (sipuleucel-T), has been engaged with the FDA for the past few years and has not yet satisfied this criterion.

The new EU regulation is attempting to create a more standardised procedure within Europe than exists in the US. The detailed consultation that is ongoing seeks to add technical bones to the regulatory skeleton established in the new regulation.

As noted above, the biological effects of ATMPs can be highly dependent on the *in vivo* environment, and may be influenced by the replacement process or the immune reaction either from the patient or the product. The respective requirements must, therefore, be investigated during clinical development, as they will have to be taken into account for the final use of the specific ATMP being considered. Also, standardisation and optimisation should be an integral part of the clinical development studies. All this influences the study design. For new ATMPs, where limited guidance exists, consultation with regulatory authorities on the clinical development plan is therefore highly recommended and the formation and involvement of specialist committees within the EMEA will be of critical importance.

A transitional period provided in Article 29 of the EU regulation stipulates that ATMPs other than tissue-engineered products legally on the community market on 30 December 2008 must comply with the regulation by no later than 30 December 2011. For tissue-engineered products the transitional period ends on 30 December 2012. Applications submitted for the authorisation of these products shall be free of charge.

The new CAT in the EU...

The EU regulation also called for the formation of the Committee on Advanced Therapies to bring together the best available expertise on ATMPs. The CAT's responsibilities are, among other things, to give advice on the classification of a given product where the classification as medical device, pharmaceutical or ATMP is in question, to evaluate ATMPs with regard to their safety or efficacy and to contribute to the development of scientific advice in the area of ATMPs and their respective safety standards. The CAT has an advisory function only. Like the European Medicines Agency, it is not a decision-making body. All decisions made under the regulation are made by the

European Commission and as a consequence are subject to legal review/oversight by the Court of First Instance in Luxembourg.

The CAT's input regarding prospective applicants for authorisations for ATMPs is likely to be key. In the US, one feature of the FDA's system that is highly valued by prospective applicants is the advice given in pre-IND meetings. This advice can be invaluable in guiding applicants into the correct design for pivotal clinical studies and can give an early indication of the adequacy of the nonclinical and early clinical data already generated, such that any perceived defects can be remedied at an early stage. It is hoped that the CAT will provide prospective applicants with a similar source of advice and will permit them at an early stage to design their clinical studies to ensure a smooth regulatory path moving forward. In an area such as ATMPs, where the products might be inherently variable due to the use of a patient's own tissue in the product, such input for design of clinical studies is critical.

The CAT will ideally offer prospective applicants for the approval of ATMPs within Europe the same comfort that the FDA Special Protocol Assessment procedure provides. The SPA procedure is seen in the US as an important part of a prospective applicant's due diligence in reducing the risk that any significant obstacles lie in wait late on in the regulatory process. The CAT will be called upon to provide such reassurance via both the scientific advice procedure to advise on the design and adequacy of clinical study design, and the certification of early-stage data.

The new regulation provides the opportunity for prospective applicants to approach the EMEA and obtain certification for their quality and nonclinical data. It is anticipated that the CAT will also play a key role in this process. The reassurance given through this certification is likely to become an obligatory part of a responsible company's regulatory risk management.

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Combination products

Combination products that have a medical device element as well as a cellular or tissue component are evaluated by the EMEA alone, which then grants EU-wide marketing authorisations under the centralised procedure. Approval for combination products rests with the EMEA, which may also request any results from a qualified body that has previously assessed the product. If no such results are available, the EMEA may commission a notified body to assess the product in conjunction with the centralised EMEA application process. The involvement of a notified body, however, is not required where the CAT feels it has sufficient expertise to perform the assessment on its own. The submission of combined products to the centralised procedure also aims to avoid classification problems that could lead to uncertainties as to which legal framework is to be applied, namely the framework for medical devices only or the framework for advanced therapies.

Again, this co-ordinated approach to the approval of such combination products is likely to mean that the approval of combined ATMP/device products will be simplified within Europe.

The EMEA may choose to involve notified bodies when assessing combination products with a device component

Postauthorisation requirements

The EU regulation creates a mechanism for reporting and documenting adverse reactions and issues involving efficacy for ATMPs after they are approved and available for public use. This is a key component in monitoring the safety of ATMPs. As a result, manufacturers will be required to file an EU Risk Management Plan as described in the Guideline on Risk Management Systems for Medicinal Products for Human Use⁷. Long-term safety issues, such as infections, immunogenicity/immunosuppressant and malignant transformation, as well as the *in vivo* durability of the associated medicinal device/biomaterial component, must be addressed in the RMP. The European Commission may, as part of the market authorisation, require that the risk management system be set up in a specific way to ensure its efficiency and safety. The EMEA with the assistance of the CAT will give guidance to the commission in this respect. The decision taken by the commission in the product authorisation is binding upon the manufacturer and product authorisation holder. It can, however, be appealed to the Court of First Instance.

As ATMPs are designed and designated to remain in the human body for a long, if not indefinite, period of time, a system allowing complete traceability of the patient as well as the product and its starting point is crucial to monitor their safety. The establishment and maintenance of the system must follow the rules and regulations set out in Directive 2004/23/EC in respect of human tissues and cells and in Directive 2002/98/EC for the collection, testing, processing, storage and distribution of human blood and blood compounds⁸. Traceability along the donor-product-recipient axis or between product-recipient for autologous products is required in all circumstances. Article 14 (4) of the regulation requires the EMEA to draw up detailed guidelines on the postauthorisation follow-up of efficacy, adverse reactions and risk management. A draft guideline was published most recently by the EMEA on 6 May 2008⁹. As noted above, such guidelines are currently in varying states of adoption and consultation.

Any manufacturer of ATMPs that does not closely follow those safety rules and standards, including those specified in the product authorisation at stake, is exposing itself to responsibility

Manufacturers will be required to file an EU Risk Management Plan

under product liability, if an adverse event occurs. The general guidelines on risk management for ATMPs envisage that approvals for such products are likely to contain many more bespoke conditions with which the applicant subsequently needs to comply postauthorisation. Such conditional approvals, where an acceptable level of compliance with such conditions is not likely to be established practice, will lead to interesting issues in product liability cases.

Ethical issues & SMEs

ATMPs are associated with high levels of public interest and issues under constant societal debate. In particular, strong resistance to the use of embryos as sources of therapeutic products demands appropriate caution and sensitivity. In light of this, the regulation does not impose EU-wide ethical guidelines. Instead, it provides that decisions regarding whether certain ATMPs will be available in a member state will be left to the member state itself.

Article 18 of the regulation provides that SMEs developing ATMPs may submit to the EMEA quality and, where available, nonclinical data, for specific evaluation and certification. For reasons of coherence and transparency it is proposed the definition of micro, small and medium-sized enterprises provided in Commission Recommendation 2003/361/EC¹⁰ should apply. The certification procedure is likely to be independent from any application for marketing authorisation. The procedure will help to strengthen the development of new ATMPs and to encourage SMEs to contribute to this development. The certification procedure prepares the applicant's data package for product authorisation and is performed for SMEs at a lower cost by the EMEA.

In this respect the new regulation provides similar assistance by way of reduced fees to SMEs, as does the US regime. Thus, both systems recognise the importance of SMEs as key drivers of innovation within the new ATMP sector.

Conclusion

The new regulation on ATMPs has closed a gap in the EU regulatory framework. It provides for a consistent legal system governing the collection, testing, processing, storage and distribution of human tissues, cells and blood and the manufacturing of ATMPs made from human materials, as well as the postauthorisation and postmarketing safety aspects relating to this specific type of product. The European regulation is similar to the regulatory framework set up in the US under the authority of the FDA, although it is much more standardised, systematic and comprehensive. One point of interest will be to review whether this standardised strategy is successful in Europe, given that it is very much the type of approach the FDA has decided is not easily applied to products such as ATMPs.

The EMEA will continue to advise manufacturers and other stakeholders on how to make use of this legal framework, and it remains to be seen how efficiently it will be implemented, used, and further refined over time. Further guidance from the commission is expected with regard to the implementation of the regulation and practice will show where further amendments and guidance will be needed. It is clear that the role of the CAT within the new ATMP regulatory regime will be vital. The CAT is likely to be the cornerstone of the efficacy and flexibility of the European ATMP regulatory regime. Its first actions will be viewed with intense interest.

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References

1. Brady R et al, Tissue Issues, *BioProcess International*, 20 June 2005, http://pharmalicensing.com/public/articles/view/1155809213_44e43fbdcd0c
2. Regulation (EC) No 1394/2007, *OJ*, 10 December 2007, **L324**, 121-137, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:EN:PDF>
3. Directive 2004/23/EC, *OJ*, 7 April 2004, **L102**, 48-58, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:EN:PDF>
4. Directive 2001/83/EC, *OJ*, 28 November 2001, **L311**, 67-128, as amended, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_83_cons/dir2001_83_cons_en.pdf
5. Guideline on Human Cell-Based Medicinal Products, EMEA/CHMP/410869/2006, 11 January 2007, www.emea.europa.eu/pdfs/human/cwpw/41086906en.pdf
6. Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products, CPMP/BWP/41450/98, 31 May 2001, www.emea.europa.eu/pdfs/human/bwp/4145098EN.pdf
7. Guideline on Risk Management Systems for Medicinal Products for Human Use, EMEA/CHMP/96268/2005, 14 November 2005, www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf
8. Directive 2002/98/EC, *OJ*, 8 February 2003, **L33**, 30-40, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF>
9. Guideline on Safety and Efficacy Follow-Up – Risk Management of Advanced Therapy Medicinal Products, EMEA/149995/2008, 6 May 2008, www.emea.europa.eu/pdfs/human/advancedtherapies/14999508en.pdf
10. Commission Recommendation 2003/361/EC, *OJ*, 20 May 2003, **L124**, 36-41, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:124:0036:0041:EN:PDF>

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The EU's framework is more standardised, systematic and comprehensive than that in the US