

Advanced Therapies Regulation

Anthony Warnock Smith and Natalie Kingston at Morgan Lewis examine the Advanced Therapies Regulation, which was finally introduced by the European Commission in November 2007

Regulation (EC) No 1394/2007 aims to standardise the regulation of advanced therapy medicinal products (ATMPs) by providing a working definition for ATMPs and introducing special rules to control such products. Until now, ATMPs have largely fallen through the cracks of the existing medicine and medical device regimes in Europe, resulting in uncertainty for the companies involved in researching and developing these products as to the correct regulatory regime for their products, as well as raising broader public concerns regarding the ethics, safety and validity of these products in their designated treatments. The Regulation aims to address these concerns and provide a clear regulatory pathway for ATMPs, and will apply throughout the EU from 30th December 2008. However, any products falling within the definition of an ATMP under the Regulation which were legally on the market on 30 December 2008 have until 30 December 2009 to comply with the requirements of the Regulation.

ADVANCED THERAPY MEDICINAL PRODUCTS DEFINED

Under the Regulation, the concept of an ATMP is broadly defined in order to capture three specific categories of advanced therapies – tissue engineered products, gene therapy medicinal products and somatic cell therapy medicinal products – with ATMPs described as any medicinal product for human use falling within one of these categories. The definitions of gene therapy medicinal products and somatic cell medicinal products are taken directly from Part IV of Annex I to Directive 2001/83/EC on the Community Code relating to medicinal products for human use, as amended (the Medicines Directive). Both gene therapy and somatic cell therapy products involve the insertion of genes and cells respectively into the human body, which have been altered in order to produce a therapeutic, diagnostic or preventative effect.

The Regulation also applies to tissue engineered products, which use a combination of cells, materials, engineering, biochemical and physio-chemical factors to create products aimed at regenerating, repairing or replacing portions of or whole tissues in the human body. The Regulation provides a lengthy definition that is broadly consistent with the above, and goes on to add that such products may contain cells or tissues of human or animal origin, or both, as well as additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices. The cells or tissues may be viable or non-viable. However, products consisting only of non-viable cells and/or tissues and which do not act principally by pharmacological, immunological or metabolic action, are excluded from the definition.

‘Engineering’, according to the Regulation, means that the cells or tissues must have been either subject to substantial manipulation, or not intended to be used for the same function in the recipient as in the donor. In terms of defining ‘substantial manipulation’, the Regulation provides a negative list of relatively standard processes which would not amount to substantial manipulation, such as cutting, grinding, sterilisation, freezing and vitrification. The Regulation also establishes rules to address any potential overlap between the three categories of products: somatic cell therapy products, which also fall within the definition of tissue engineered products, must be treated as tissue engineered products, and products which could fall under any of the three definitions will be considered gene therapy products.

COMBINATION PRODUCTS

One characteristic of the technology and innovation surrounding ATMPs acknowledged in the new legislation is that they can be made up of a combination

of medicinal products and medical devices. This is a further grey area under the existing medicines/medical devices regime that often led to products – which should otherwise have been treated as medicinal products due to their advanced pharmacological or physiological functions – falling under the definition of a medical device (due to the device being the primary function of the product) and, thus, failing to be properly regulated.

The Regulation addresses this by providing a definition for ‘combined advanced therapy medicinal products’, namely ATMPs which incorporate one or more medical devices (as defined by Directive 93/42/EEC on medical devices), or one or more active implantable medical device (as defined by Directive 90/385/EEC on active implantable medical devices); and which contain in their cellular or tissue part either viable cells or tissues, or non-viable cells or tissue which must be liable to act upon the human body with an action that can be considered as primary to the device(s).

AUTHORISATION OF ADVANCED THERAPY MEDICINAL PRODUCTS

The Regulation dictates that all ATMPs are to be authorised via the centralised procedure in accordance with Regulation (EC) No 726/2004, laying down community procedures for the authorisation and supervision of medicinal products for human use (the Medicines Regulation).

A new committee – the Committee for Advanced Therapies – is also established by the Regulation which will, amongst other responsibilities, take part in the evaluation procedure for applications for ATMPs. The Committee for Medicinal Products for Human Use will be required to consult the Committee for Advanced Therapies on any scientific assessments concerning the evaluation of an ATMP marketing authorisation application. Additionally, where medical devices

and/or active medical devices are incorporated into an ATMP, the devices must meet the essential requirements laid down in their respective Directives, and the appropriate assessment results from a notified body must be included in the marketing authorisation application for any combined ATMPs. Such products containing medical devices, bio-materials, scaffolds or matrices must also include, as part of the marketing authorisation application, a description of the physical characteristics and performance of the product and a description of the product design methods, in accordance with Annex I of the Medicines Directive.

INCENTIVES/POST AUTHORISATION REQUIREMENTS

There are various incentives (predominantly fee reductions) introduced by the Regulation that are available either to all applicants or to small- and medium- sized enterprises. These include advice from the EMEA on the design and conduct of a pharmacovigilance and a risk management system for an ATMP; advice as to whether the product being developed falls, on scientific grounds, within the definition of an advanced therapy medicinal product; certification of the quality and non-clinical data required to be submitted with an application (SMEs only); and a 50 per cent reduction on the fee for marketing authorisations (SMEs and hospitals only) for products which can be shown to have a particular public health interest.

Once an ATMP authorisation has been granted, there are also a number of specific rules and requirements introduced by the Regulation, covering labelling, the summary of product characteristics, packaging, post-authorisation follow-up and traceability.

INDUSTRY REACTION TO THE REGULATION

Prior to the official publication of the Regulation, there was much discussion and debate by interested parties as to what the definition of an ATMP should include or exclude, how various products should be regulated and what the correct regulatory regime should be. The debate focused predominantly on the ethical issues surrounding ATMPs. Human stem cell research remains a controversial topic,

About the author



Anthony Warnock-Smith is a Partner who leads the life sciences practice in the London office of international law firm Morgan Lewis. His practice focuses on government regulation, business transactions involving the pharmaceutical, medical device, cosmetics, veterinary drug, and foods and food additives industries. His government regulation experience involves the full range of services of interest to these industries, from clinical trial and product development issues, to marketing and allied reimbursement, product liability and other trade regulation matters. He has also worked on joint ventures, mergers and acquisitions, EU competition law, restructurings, distribution agreements, technology licensing and strategic partnering for these industries. [Email:](#)



Natalie Kingston is an Associate in Morgan Lewis' business and finance practice and is a member of the Global Outsourcing Group. Natalie handles a wide range of regulatory matters, commercial agreements and transactions for clients in the life sciences sector. In addition to acting for pharmaceutical and medical device companies, she also has particular experience advising in relation to foods and cosmetics. Natalie is involved with outsourcing and general commercial and corporate issues including joint ventures, intellectual property and technology agreements. [Email:](#)

although proposals to leave human embryonic stem cells outside the Regulation were eventually rejected. Instead, the Regulation follows the already existing EU rules for the ethical donation, testing and procurement of human cells or tissues (which are expanded in Directive 2004/23/EC).

However, there is the potential for individual EU Member States to somewhat restrict the application of the Regulation. Article 28(3) of the Regulation, which amends the Medicines Directive, provides that the Medicines Directive (and any Regulations referred to therein, including this Regulation) will not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from such cells. As such, there is scope for one or more Member States to introduce national legislation which could limit, or indeed expand upon the scope and harmonised use of the Regulation by introducing national rules which are divergent with its principles.

CONCLUSION

Since its publication, the industry has had some time to digest and prepare for the

implementation of the Regulation later this year. However, as with most new European legislation, many will withhold judgment until the changes are implemented. While there are undoubtedly some parties concerned by a more onerous regulatory burden, at the very least the Regulation has provided a structured framework for companies developing ATMPs to follow that will no doubt assist in future research and development strategies.

Meanwhile, the European Commission has been busy itself preparing for the implementation of the Regulation. It contains a number of key tasks for the EC to complete in order to ensure the successful implementation of the Regulation. Accordingly, the EC has published an implementation plan setting down its priorities for the enactment of the Regulation. Priorities listed in the plan include amending Annex I of the Medicines Directive to include a description of the physical characteristics, performance and product design methods which should be included in marketing authorisation applications for ATMPs, and preparing guidelines on good clinical practice, good manufacturing practice and traceability requirements for ATMPs. This will no doubt provide further enlightenment on the operation of the Regulation.