

# Redefining medicine

**A new European law is set to accelerate the deployment of highly sophisticated medicinal products based on genes, cells and tissues by giving them a privileged status which also guarantees quality**

As the search for blockbusters grows more desperate, the law is expanding to accommodate a new class of product. From 30 December 2008, the expression 'medicinal product' will encompass things made using human or animal cells. Like 'gene therapy medicinal products' and 'somatic cell medicinal products', such tissue-engineered products (TEPs) will fall within a special class: 'advanced therapy medicinal products' (ATMPs). Together they will enjoy a privileged status under European medicines law.

The Advanced Therapies Medicinal Products Regulation aims to boost development of personalised, regenerative and nano medicines while guaranteeing a high level of quality and safety. This is the most important and the most revolutionary piece of European medicines legislation of the 21st Century. It will apply in every member state.

## AIMS AND MEANS

Modern biotechnology has produced so many new genres of medicinal products so quickly that the law has not kept up. Products made using tissues such as skin, cartilage or bone have not sat easily within the existing device/medicine framework. A product could be classified as a device in one state and as a medicinal product in another - presenting a considerable impediment to marketing a tissue-engineered product across Europe. The Regulation unifies the classification rules, attempting to proof them against future technical advances, providing a centralised procedure for authorisation on

the European market and adding powerful incentives.

It also recognises that developers are often small- and medium-sized enterprises and hospitals, rather than large pharma companies. However, rather than establishing a new 'third pillar' framework for advanced therapies to sit alongside those for devices and medicines, it exploits existing rules and institutions. Specifically, it amends the Medicinal Products Directive (2001/83) and Regulation on the Authorisation and Supervision of Medical Products in the Community (726/2004). From now on, advanced therapies are medicines. In many cases, they will also be devices.

## DEFINING ATMPs

The ATMP Regulation lays down rules for the authorisation, supervision and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products and TEPs. As the first two members of the family are defined, the Regulation's first job is to define TEPs. Broadly speaking, they sit between two excluded extremes: cell grafts and devices which lack pharmacological, immunological or metabolic action. At the root of the old classification problem was the "principal mode of action" rule that separates devices from products. The Regulation ensures eligibility as a medicinal product. Even if the device aspect is dominant, the pharmacological, immunological or metabolic action of any viable cells/tissues will be deemed to be the principal mode of action.

The Regulation's definition of TEP encapsulates products presented as having properties for regenerating, repairing or replacing a human tissue and which contain or consist of cells or tissues: human, animal or both. TEPs may include additional substances, such as chemicals, scaffolds, matrices and non-viable cells. However, products containing no viable cells at all and which do not act principally by pharmacological, immunological or metabolic action are excluded. Crucially, the constituent cells or tissues must be 'engineered'. This means that they are either "subject to substantial manipulations" - which means rather more than cutting, grinding and various other acts - or that they are not intended to be used in the same way in the donor as in the recipient.

An ATMP integrated with one or more 'medical device' (or 'active implantable medical device' as defined in relevant directives) where cell/tissues are viable or act primarily as a device is called a 'combined ATMP' and will be regulated as a medicine and as the appropriate device.

Finally, the Regulation provides a cascade approach to borderline cases. If a product could be classified as a TEP or a somatic cell medicinal product, it will be deemed a TEP, but if it could be a gene therapy medicinal product, then that status will prevail.

## MARKET AUTHORISATION

The ATMP is primarily a law of market authorisation. However, no ATMP will be authorised unless other conditions,

## In Brief

### S-A generics agreed

Sanofi-aventis has agreed to allow the sale of generic versions of some of its allergy drugs in return for royalties. The agreement settles a three-year US patent infringement suit issued against generic manufacturers Barr Pharmaceuticals and Teva Pharmaceuticals. The agreement states that in exchange for royalties, Barr and Teva can

sell cheaper versions of the allergy drugs Allegra and Nasacort in the US. Royalties are to be applied to sales retrospectively. Under the terms of the agreement, Barr will have an option to purchase the finished pharmaceutical product from sanofi-aventis on a non-exclusive basis. In 2007, US sales of Allegra and Nasacort totalled \$276m and \$301m, respectively. Sanofi-aventis is continuing with ongoing patent infringement suits against other generic manufacturers.

### Marketing harmony

Irene Sacristan Sanchez, European Commission Enterprise and Industry DG, has announced that proposed regulation aimed at harmonising rules on marketing authorisations of medicines in the EU will be published later this month and be effective in 2009. The EC has been working on a global revision of the legal framework governing variations in the terms of marketing authorisations to make the system clearer, simpler and

more flexible. Speaking at the third annual EMEA Legislation Update - hosted by TOPRA (the Organisation for Professionals in Regulatory Affairs) and the EMEA in London in early December - Ms Sacristan Sanchez also said three legal proposals would be announced shortly to reduce the risk of counterfeit medicines reaching the supply chain, improve pharma's ability to communicate with patients and provide stronger public health protection with clearer rules on pharmacovigilance.

set out in EU rules are met. First, the donation, procurement and testing of cells comprised with the product must accord with the requirements of the Tissue Cell Directive (2004/23). Second, clinical trials of all ATMPs must be in accordance with the rules which are already applicable to gene therapy and somatic cell therapy medicinal products (Directive 2001/20) and with the Commission's new good clinical practice guidelines. Third, products must comply with the GMP Directive (2003/94) and the Commission's new GMP guidelines for ATMPs. Fourth, all constituent medical devices and active implantable medical devices of combined ATMPs must comply with the relevant directive (93/42 or 90/385) and the application for authorisation must include a description of the product's physical characteristics, performance and design methods.

## CENTRALISED PROCEDURE

All other modern biomedical products regulated at EU level are subject to a centralised authorisation procedure, involving a single scientific evaluation of the quality, safety and efficacy of the product, carried out to the highest standard by the European Medicines Agency (EMA). The Regulation makes this centralised procedure not only possible, but compulsory for ATMPs.

This opens up an entire EU market in ATMPs; a huge improvement made all the sweeter for small and medium-sized enterprises (SMEs) and hospitals by half-price authorisation fees. In part, however, the requirement for the centralised procedure is an acknowledgment of the scarcity of relevant expertise; which the Regulation concentrates in a new EMA Committee for Advanced Therapies (CAT). CAT will produce opinions on all applications to market ATMPs, which the EMA's Committee for Medicinal Products for Human Use (CHMP) must consider before giving approval.

Combined ATMPs will be regulated, not only as ATMPs, but as one or more medical device or active implantable medical device. The EMA makes its final evaluation for authorisation of such combined ATMPs by considering the whole product, with evidence of device conformity.

## REQUIREMENTS

Unlike conventional medicinal products, many ATMPs become part of the recipient's body. This demands the toughest standards of supervision, especially regarding the demonstration of quality, safety and efficacy. The traceability requirements introduced pursuant to the Tissue/Cell Directive are

extended to ATMPs and bulked up with new EC guidelines to ensure that the product and its starting and raw materials - including all substances coming into contact with the cells or tissues it may contain - can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where it is used. Demands upon the summary of product characteristics, package leaflet and labelling are also cranked up: immediate packaging must bear the unique donation code and product codes required under the Tissue/Cell Directive and, in the case of products intended for autologous use, the unique patient identifier and the statement "For autologous use only".

"This is the most revolutionary piece of EU medicines legislation of the 21st Century"

Pharmacovigilance standards are also elevated, obliging ATMP applicants to provide details of the measures they envisage to ensure the follow-up of efficacy and adverse reactions. If there is a particular concern, the EC may, on the EMA's advice, require systems to be set up to identify, characterise, prevent or minimise risk. Alternatively, it can require specific post-marketing studies. The EMA will advise applicants and marketing authorisation-holders on the design of such pharmacovigilance and risk-management systems.

## INCENTIVES

Standard EMA product evaluation fees are cut by 90 per cent for SMEs, with a 65 per cent reduction in other cases. The EMA will, on request, provide (through CAT) opinions as to whether candidate products fall within the definition of an ATMP. The price is publication of the recommendations: although the EMA delete confidential commercial information, many developers will want anonymity. SME developers may also submit quality and non-clinical data to the EMA for scientific evaluation and certification, independent of any application for marketing authorisation. Certification is not legally binding, but it is hoped that the system will ease applications for clinical trials and marketing authorisation using the same data. Finally, the Regulation halves the fees for marketing authorisation, payable

by SMEs and hospitals, if they can prove that the EU has a particular public health interest in the ATMP concerned. The same reduction applies to EMA fees payable in the year after marketing authorisation.

## HOSPITAL EXEMPTION

Having swept ATMPs into the control of the Medicinal Products Directive, the Regulation then exempts those that are "prepared on a non-routine basis according to specific quality standards, and used within the same member state in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient".

The manufacture of such products must, nevertheless, comply with the EMA's GMP standard and be authorised by the competent authority of the member state, which must also ensure compliance with device legislation, good clinical practice and pharmacovigilance. The requirements of cell donation, procurement and testing, and the rules as to traceability, also continue to apply.

## THE EMBRYO GAP

Following bitter debate in the European Parliament, the ATMP Regulation provides a moral opt-out for states whose national legislation prohibits or restricts 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 these cells. Given the importance of embryos to provided pluripotent cells, this seems inconvenient. However, because the EC has to publish the relevant legislation of all member states, it effectively assures an accurate stem cell map for patients and business. As therapies come on stream, "no-rated" states will either mitigate their economic and humanitarian stigma with a glow of self-righteousness or change their tune.

## THE WAY FORWARD

The ATMP provides reasons to invest in regenerative and other advanced therapies. For European businesses to flourish, however, they must also make headway with FDA regulations. Increased transatlantic co-ordination on GMP matters may add a further economic boost. By 30 December 2012, the Commission will publish a progress report on the Regulation, with comprehensive information on each type of ATMP and a review of the scope of the Regulation, especially as regards combined ATMPs.

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