The European Commission’s proposal for a Regulation on Advanced Therapy Medicinal Products (ATPs) is a significant step towards EU-wide harmonisation, clarity and certainty for tissue engineered products. But the new clarity comes at a significant cost to the medical devices industry, Project director at Voisin Consulting, Dr. Anne Dupraz Poiseau comments in collaboration with colleagues, consultant Isabelle Mingam, and senior consultant Dr. Stuart Mudge.

The proposed Advanced Therapy Medicinal Products (ATPs) Regulation helps to clarify borderline issues and represents a significant step forwards towards finally achieving a rapid harmonised path to the market for these innovative and promising products. The proposed text contains some incentives for the medical devices industry which is responsible for producing the majority of products in this field, but it also has a number of features that are going to severely challenge the sector as it adapts to a regulatory framework that is much more in line with that of the pharmaceutical industry.

The need for an establishment licence, a qualified person for batch release, and the obligation to adapt existing quality management and vigilance systems to a more pharmaceutical-oriented regulatory framework are all new hurdles. And while the European Commission has taken into account the results of extensive public consultation (May to June 2005) and has introduced measures that address many of the specific requirements associated with TEPs, the success of this regulatory framework will rest heavily on the quality of the guidelines that are to be written through the standard “comitology” process.

Other specific requirements that have been introduced include an emphasis on risk management and traceability, the reinstatement of xenogenic TEPs within the scope of the proposed Regulation, and tailored rules for clinical trials and manufacturing practices.

The medical devices industry understandably has concerns regarding the perceived pharmaceutical bias of the framework; however it does bring some advantages that were not previously available to the medical device industry.

The legislative framework described by Regulation 726/2004/EC for centralised authorisation (via EMEA) and supervision of medicinal products will: (i) allow the marketing authorisation holder (MAH) to benefit from an “8+2+1” year data protection period from generics throughout the entire EU; (ii) provide the possibility of orphan designation and accelerated or conditional approval; (iii) bring a 90% reduction in the fees for EMEA scientific advice; and (iv) access to special incentives for SMEs in accordance with Article 70 section 2 and the consultation paper of 14 October 2004*.

The fee reduction for scientific advice should not be underestimated and is critical to the success of the ATP framework: it provides access to the full breadth of scientific
expertise at the EU level, encourages close collaboration between the EMEA and product developers, and will help to ensure the ATP Regulation is adapted and revised on an ongoing basis to ensure it matches the rate of evolution in this extremely innovative field.

Another big plus which is truly welcome and has the potential to provide a real selling point for SMEs developing ATPs in the out-licensing of products for further development is the EC proposal for the possibility of granting such SMEs a certificate of quality and/or pre-clinical safety.

All these advantages for the medical devices come with a price to pay: within the ATP regulatory framework the authorization process will involve a 210-day assessment procedure, a major disincentive for medical device-oriented companies given that even in the case of high-risk devices there is a maximum of a 90-day compliance assessment by the notified bodies.

In addition, it will be mandatory to register ATPs via a centralised procedure application to the European Medicines Agency (EMEA), a regulatory pathway radically different from the so-called “New Approach” procedures for CE marking (based on risk management and standardisation), with which companies developing medical devices are familiar.

It must also be noted that this new regulatory framework will pose problems for the European Medicines Evaluation Agency, the EMEA, and its ability to adapt will be critical. The EMEA has strong experience and expertise in medicinal products but not in medical devices. The EMEA does not speak the same language as medical device manufacturers and this must be considered as a significant obstacle to the success of the ATP framework. Clearly the EMEA must add medical device, engineering and risk management expertise to its structure.

The Regulation foresees the creation of a new consultative arm of the Committee for Human Medicinal Products (CHMP) at the EMEA: the Committee on Advanced Therapies (CAT). The Regulation states that the CAT shall include representation from all member states and relevant expertise to assist the CHMP in the assessment of the safety and efficacy of ATPs, including: medical devices, tissue-engineering, gene and cell therapies, biotechnologies, pharmacovigilance, risk management, and ethics.

While the CAT is welcome, it will be a major exercise in project and people management to ensure that its final composition covers the full spectrum of necessary expertise. Given the challenges the EMEA will face in adapting to the medical device arena it is vital that medical device and risk management expertise is not underrepresented on the CAT. Furthermore, although consultation of a notified body is envisaged by the Regulation for the assessment of the device component of a combined ATP one wonders what will be the extent of its jurisdiction and influence on the larger EMEA machine?

Another point of concern is the transitional period between the application of the Directive 2004/23/EC, on the setting of standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, and this proposed Regulation. Where ATPs contain human
The pros and cons of the Commission’s proposal for Advanced Therapy Products

cells or tissues, the Directive 2004/23/EC will apply for donation, procurement and testing of human cells or tissues, while the ATP Regulation applies from processing to distribution. We wonder how best to manage the transition between the entry into force of Directive 2004/23/EC (7 April 2006) and the ATP Regulation (foreseen for 2007/2008). One suggestion would be to apply Directive 2004/23/EC in full, but does this carry the risk that each ATP developer will have to be established as tissue bank?

Much of the impact of the Regulation will only be known as the guidelines are developed, details of the exact structures emerge and the system begins to take shape. But already one uncertainty is in the process of being addressed, and that is the fate of medical devices incorporating human cells or tissues in an ancillary purpose. These are not included under the scope of this proposed Regulation and there have been concerns that these would remain unregulated?

Fortunately, the Commission has considered industry comments and is currently working to address this gap by amending the Medical Devices Directive 93/42/EC to include these products under its scope**. It is now foreseen that these products would be evaluated as conventional medical devices by the notified body which would have to seek the opinion of the forthcoming Committee on Advanced Therapies (CAT) at the EMEA for the evaluation of the human cell/tissue part.

This assessment route would be the same as that already in place for the conformity assessment of medical devices incorporating blood derivatives or medicinal products approved via centralized authorisation.

The amendment is being drafted and needs still to be validated (hopefully before September 2006). If the Regulation on Advanced Therapies is not in place before the amendment of Directive 93/42/EC is passed, an option could be that the consultation procedure would simply be handled by the EMEA without the new Committee (CAT). We think this is very good news for all medical device companies working in this field.

In conclusion, with the ATP Regulation the EC has helped to clarify borderlines issues and taken a significant step forward towards finally achieving a rapid harmonized path to the market for such innovative and promising products. There is a price to pay, particularly for the medical devices industry. To ensure this price is tolerable, and does not constitute an unacceptable barrier to ATPs entering the EU market, there is a clear responsibility for all stakeholders to continue their collaborative efforts by testing the system and generating guidance documents that translate the framework of the Regulation into an effective and user friendly regulatory environment.

* Consultation paper of October 14, 2004 on provisions for micro, small and medium-sized enterprises (SMEs) establishing the circumstances in which SMEs may pay reduced fees, defer payment of the fee, or receive administrative assistance.

** Information Source: personal discussion with John BRENNAN, European Commission, Principal Administrator, Medical Devices Sector, Unit F3 - Cosmetics and Medical Devices, Directorate F - "Consumer Goods", Directorate General Enterprise and Industry; In charge of the Amendment of Directive 93/42/EC

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