



# MEDICAL DEVICE TRANSLATION NEWS

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## HTPs to be regulated as pharmaceuticals in Europe?

By Jeanette Marchant—London, UK

The prospect of a European regulatory framework for human tissue engineered products (HTPs) moved a step closer in May 2005 with the publication of a Consultation Paper by the European Commission which is designed to bridge the regulatory gap. However, the decision to include HTPs with gene therapy and somatic cell therapy in a single, integrated regulatory framework for all advanced therapies indicates a shift in thinking by the Commission towards regulating HTPs as pharmaceuticals.

Whereas products intended for gene and somatic cell therapy are already classified and regulated as medicinal products in the European Union, tissue-engineered products fall outside existing European Directives. Manufacturers of HTPs represented by the European industry associations Eucomed, EuropaBio and EBE argue that since HTPs are neither cell therapy products nor drugs—and have twice been excluded from the Medical Device Directive—they should have their own, separate and dedicated regulatory system.

The European industry advocates a new “third pillar” regulation, distinct from medical devices and medicinal products, which is geared towards the specific needs of HTPs. Following two previous consultations in 2002 and 2004, proposals along these lines had been drawn up and discussed with the Commission services. But reorganisation within the Commission in early 2005 has prompted an alternative approach in which HTPs are viewed as medicinal products from a legal standpoint.

Within the Directorate General Enterprise, medical devices and HTPs have been moved into the Consumer Goods Directorate, which also covers pharmaceuticals, food and the automotive industry (see box below). And in March 2005, the HTP file was moved from the unit covering biotechnology to the pharmaceuticals unit, reflecting the regrouping of gene and cell therapy medicinal products and human tissue engineered products under the new heading of advanced medical therapies.

European Commission Directorate General Enterprise —  
Directorate F Consumer Goods  
Director: Mme Georgette Lalès

### Unit

1. Automotive industry
2. Pharmaceuticals (Acting head: Nils Behrndt)
3. Cosmetics & medical devices (Deputy head: Abraao Carvalho)
4. Food Industry
5. Competitiveness in the Pharmaceuticals Industry & Biotechnology (acting head: Christian Siebert)

The new Consultation Paper\* on the proposed regulatory framework for advanced medical therapies envisions a Regulation which lays down ad hoc regulatory principles building on current legislation. It would establish a compulsory centralized Community marketing authorization via the European Medicines Agency (EMA). (Gene and cell therapy products currently have to use this route.) Scientific evaluation of HTPs (and other advanced medical therapies) would be carried out by a newly-created Committee for Advanced Therapies (CAT), on behalf of the Committee for Medicinal Products for Human Use (CHMP) within the EMA. An accelerated—or “fast track”—assessment procedure would be granted for products which are considered of major public health interest.

Whereas the technical requirements necessary to demonstrate quality, safety and efficacy of gene and somatic cell therapy products are already covered by existing legislation, the main technical requirements for HTPs would be developed through a “comitology” procedure, complemented by guidelines dealing with specific issues. Acknowledging that conventional pharmaceutical technical requirements are not directly relevant for advanced therapy products, the requirements for HTPs would be specific to the products concerned, for example, relating to their mechanical and physical properties.

All aspects of HTPs which include medical devices as an integral part of the product would be evaluated by the CAT, although Notified Bodies may be consulted. The medical device component should meet the essential requirements of the Medical Device Directive but would not require CE-marking.

Since the majority of companies affected by the proposed Regulation are small and medium-sized enterprises (SMEs), the Commission plans to grant a 90% fee reduction for EMA scientific advice on advanced therapies. As part of the administrative assistance offered to SMEs, the EMA will also make “appropriate arrangements” for translations of all documents (summary of product characteristics, labelling and package leaflets) which accompany the marketing authorization.

### European HTP Industry Profile

Of some 113 companies active in the field of tissue engineering which were identified in a report produced for the European Commission's DG Enterprise in October 2003, the majority are SMEs with fewer than 50 employees. Of the 113 companies, 54 were defined as core tissue engineering companies, with 48 falling into the broader category of companies which carry out activities directly related to tissue engineering such as construction of bioreactors, while the remaining 11 companies produce tissue-engineered products for in vitro use only (i.e. not for therapeutic purposes).

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The majority of companies (39) are based in Germany, followed by the UK (18), France (10) and Sweden (10). Of the 113 companies identified, 80 were biotechnology companies, 24 medical device companies and 9 pharmaceutical companies.

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The term "comitology" refers to procedures under which the Commission executes its implementing powers with the assistance of "comitology committees" consisting of Member State representatives. The Commission services submit draft implementing measures to the comitology committees for their opinions before the Commission adopts them. If the comitology committees' opinions do not confirm the draft measures, the draft may be submitted to the Council for a final decision. The comitology procedure envisaged for the adoption of technical requirements for HTPs raises questions about how much input industry would have in their development.

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The potential worldwide market for HTPs has been estimated up to €100 billion, according to the Commission report. Since the first tissue-engineered product - cartilage - was approved for marketing in 1996 in the USA, commercial products have largely been skin substitutes, knee cartilage repair and bone repair products. The lack of a European-wide regulatory framework has hindered development of the HTP industry in Europe. Currently, HTPs are regulated on a case-by-case basis, either as pharmaceuticals (as in Germany) or as medical devices (as in the UK). The differing national approaches to regulation are considered by the European Commission report to be the main reason for the predominance of autologous products in the EU since the investment required to develop and carry out clinical trials for allogeneic products for only a small national market would be too costly for most HTP companies.

To access the potential global market, the European industry needs "a specific innovation-friendly regulatory framework that ensures both patient safety and rapid patient access to new treatments," according to Eucomed, which represents the majority of companies developing HTPs in the EU.

### Differing Mode of Action

Regulating HTPs as pharmaceuticals is viewed as running counter to the Commission's aim to foster the competitiveness of companies operating in this field. The pharmaceutical regulatory system is not perceived as being geared up to HTPs, where the speed of innovation is typically higher than that of drugs or medical devices. Unlike medical devices, where the regulatory system follows the "new approach" of providing guidance to meet essential requirements, pharmaceutical legislation is prescriptive with detailed regulations. Not only is such an approach inappropriate for HTPs because of the potential diversity of products, but it does not take into account their different mode of action. Whereas the principle mode of action of a pharmaceutical product is pharma-

cological, metabolic or immunological, this is clearly not the case of the majority of HTPs, contends Eucomed.

For example, HTP skin treatment intended to provide a physical protection for serious burns while the patient's own skin gradually regenerates and human tissue-engineered cartilage intended to replace damaged cartilage have a very different primary intended mode of action to cell therapy treatments such as the injection of dopamine-secreting stem cells into the brain to treat Parkinson's disease.

"A 'one-size fits all approach' would be inappropriate and any future HTP Regulation should essentially be based on a risk management/quality control philosophy," according to Richard Moore, scientific director of Eucomed. The route that Europe is proposing to take differs from the situation in the US and Australia, where regulators do not consider HTPs to be pharmaceuticals. Australia is adopting the same stance as the US Food and Drug Administration which decides on a case-by-case basis whether to treat these products as medical devices or biologicals.

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### Examples of HTPs:

- Skin (e.g. treatment of burns or chronic ulcers)
  - Cartilage (e.g. treatment of sports injuries, arthritis)
  - Bone (e.g. treatment of trauma, reconstructive surgery)
  - Blood vessels (e.g. vascular surgery)
  - Nerves (e.g. restoration of neural function)
  - Cardiac muscle (e.g. regeneration of diseased tissue)
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### Timetable

The consultation period on the proposed EU regulatory framework on advanced therapies closes on June 20, 2005. Mme Georgette Lalis, director of the Consumer Goods Directorate, has indicated that an official proposal for a Regulation will be submitted to the European Council and Parliament in September 2005. The Commission's hope that the proposal will attract the least possible resistance from the European Parliament (EP) may be optimistic, according to Joseph Putzeys, who was instrumental in drafting the medical device directives at the European Commission and is now an independent consultant. Speaking at Eucomed's technical forum in Brussels in April, Putzeys said he believed that an "empty" framework was unlikely to be accepted by the EP without MEPs being closely involved in its development.

The development of HTP regulations has wider implications for new technologies in the pipeline. "What happens here could be very important for what happens afterwards with new innovative technologies such as nanomedicine. Will they be shifted for convenience into some existing [regulation] or will they be properly analysed and placed where they can reach the market quickly?" questions Moore.

\* Consultation Paper is available from <http://pharmacos.eudra.org/F2/advtherapies/index.htm>

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