REGULATORY RESEARCH

***Question**: When will the Advanced Therapies regulation be implemented in the EU and specifically in Spain?*

SUMMARY

Background and Definitions

Advanced Therapy medicinal product means any of the following medicinal products for human use:

- a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a tissue engineered product (still being defined)
  - contains or consists of engineered cells or tissues, and
  - is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue.

EU Status

The current lack of an EU-wide framework leads to divergent national approaches as to the legal classification and authorization of advanced therapy products.

Key Elements of New Regulation

- The key elements of the new regulation include
  - a centralised marketing authorisation procedure;
  - the establishment of an expert committee within the European Medicines Agency (EMEA) to scientifically evaluate, assess and monitor these advanced therapy products;
  - technical requirements that are tailored to the therapies;
  - strengthened requirements for risk management and traceability; and
  - incentives for small and medium enterprises (SMEs).
- This Regulation is a lex specialis, which introduces additional provisions to those laid down in Directive 2001/83/EC. The scope of this Regulation should be to regulate advanced therapy medicinal products which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.
- Advanced therapy medicinal products should be subject to the same regulatory principles as other types of biotechnology medicinal products. However, technical requirements, in particular the type and amount of quality, pre-clinical and clinical data necessary to demonstrate the quality, safety and efficacy of the product, may be highly specific.
  While those requirements are already laid down in Annex I to Directive 2001/83/EC for gene therapy medicinal products and somatic cell therapy medicinal products, they need to be established for tissue engineered products. This should be done through a procedure that provides for sufficient flexibility, so as to easily accommodate the rapid evolution of science and technology.
- This legislation will provide for a single, consistent regulatory framework for gene-therapy, cell-therapy and tissue-engineered products in Europe. It will ensure that the safety, effectiveness and quality of such products be evaluated by a competent committee comprised of the best experts in the EU and that such innovative treatments are made available to European patients on the European market.

Principal Mode of Action

- When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action.
- According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product.

Combination Products

- Advanced therapy medicinal products may incorporate medical devices or active implantable medical devices. Those devices should meet the essential requirements laid down in Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.

Clinical Trials

- Clinical trials on advanced therapy medicinal products should be conducted in accordance with the overarching principles and the ethical requirements laid down in Directive 2001/20/EC of of 4 April 2001. However, tailored rules should be laid down, adapting Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products, in order to fully take into account the specific technical characteristics of advanced therapy medicinal products.
- An Ethics Committee for traditional drugs needs to issue an opinion within 60 days of receipt a valid application. A time extension of 30 days for gene therapy, cell therapy, and genetically modified organisms days is allowed. In addition, a delay of 90 additional days may be applied if the Ethics committee consults a committee of experts. No time limit is foreseen for xenogenic cell therapy products.
- For traditional drugs, a clinical trial can be initiated 60 days after submission of a valid dossier to the competent regulatory authority, provided that the regulatory authority does not notify applicant grounds for non-acceptance. In case of objection, the clock stops and the sponsor has to submit his answer/amendment to his original request. If the amendment is not supplied, the application is rejected. Exceptions are foreseen for gene therapy and cell therapy products, genetically modified organisms and xenogenic cell therapy medicinal products for which a national regulatory written authorization shall be required. The timescale of the procedure is 90 days, which may be extended by a further 90 days if experts are consulted.

Traceability

- A system allowing complete traceability of the patient as well as of the product and its starting materials is essential to monitor the safety of advanced therapy medicinal products. The establishment and maintenance of that system should be done in such a way as to ensure coherence and compatibility with traceability requirements laid down in Directive 2004/23/EC in respect of human tissues and cells.
- The traceability system should also respect the provisions laid down in Directive 95/46/EC of 24 October 1995 on the protection of individuals with regard to the processing of personal data and the free movement of such data18

Stem Cell Lines

- Currently, decisions on the use or prohibition of any type of cells, including embryonic stem cells, are a national responsibility. This is fully in line with the Directive on the quality and safety of human tissues and cells (Directive 2004/23/EC).

Timeline

- 16 November 2005 - EU Commission submitted its proposal for a Regulation on advanced therapy medicinal products to the Council and the European Parliament on
- 25 April 2007 - European Parliament votes for ADT
- 16 May 2007 - all delegations indicated that they could vote in favor of the text in the Annex with the exception of the **Spanish delegation**, which maintained its reservation of substance on the so called "hospital exemption" (Article 28, Point (1)).
- May 31 2007 – First reading agreement achieved by all Member States. Next steps: the Regulation now needs to be translated in all EU official languages, checked by the linguistic revisers of the Council/European Parliament, and formally adopted, signed and published. This purely formal and administrative procedure should take a couple of months.
- **Estimated implementation date** of January 2008, however, another source indicated the new Advanced Therapies regulation will apply in all countries of the EU one year after entry into force; in practice, this will mean mid-2008 (http://www.phgfoundation.org/news/3313).

References:

1 Proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

2 Directive 2004/23/EC, which lays down basic quality/safety requirements on human tissues and cells