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Current Intelligence

General

Advanced therapies and the outer limits of DNA regulation: new horizons for patents or a scaffold too far?

EC Regulation 1394/2007 on advanced therapy medicinal products and amending EC Directive 2001/83 and EC Regulation 726/2004

This Regulation seeks to regulate existing and future advanced therapy medicinal products intended for the market in Member States, being either prepared industrially or manufactured by a method involving an industrial process, and introduces additional provisions to those laid down in the pharmaceutical legislation Directive 2001/83.

Legal context

On 25 April 2007, the European Parliament voted in first reading on the Commission proposal for a Regulation on advanced therapy medicinal products, the proposal being based on Article 95 of the Treaty. Five weeks later, the Council of Ministers approved the Regulation on advanced therapies and amending Directive 2001/83 and Regulation 726/2004, in first readings. The completion of the formalities of translation and adoption were posted on 30 October 2007; signing and publication were completed 10 December 2007. The Regulation 1394/2007, will apply from 30 December 2008.

This category of therapeutics will now be covered by a Regulation. It may appear surprising that a centralized approach is favoured, not least given recent political controversies over other ethically contentious areas such as abortion in Poland. However, the most important aspects of the unique regulatory framework nominated by the Commission will be to attenuate the significant potential health risks associated with tissue-engineered products (TEPs) and to provide legal clarity for these highly specific therapies. Europhiles will be encouraged by the broad consensus in favour of a specific, harmonized, and coherent EU regulatory framework covering TEPs, as well as other cell-/tissue-based products.

Facts

Within the European Medicines Agency (EMEA), there will be established a new body of experts—the Committee for Advanced Therapies (CAT)—who will provide ongoing oversight on therapies, for final approval by the Committee for Medicinal Products for Human Use of the Agency, as they are submitted in a marketing authorization application. The EMEA must provide a scientific justification, should it wish to disregard the opinion of the CAT for any given product authorization application.

The Regulation will help to overcome the threat to patient health posed by the lack of a critical mass of experts in the field in many Member States; pooling of expertise will enhance the efficacy of the approval process, minimize risk to patients, and facilitate speedier access to the EU market. During the extensive consultations preceding the formulation of the Draft Regulation however, concern was raised over the potential issue of confidentiality and conflicts of interest between regulators and applicants, in a scientific area where regulatory competence is in short supply. The specialized nature of these products is to be reflected in a tailor-made centralized regulatory evaluation, this being part of an approach familiar for biological and non-standard pharmaceutical products, a process which the EMEA has comprehensively carried out for some two decades. While there has been little or no market penetration of such therapies, it is too early to correlate this dearth of product with the preponderance of 27 differing regulatory systems across the EU. However, a unified evaluation and direct access to the community market will facilitate enhanced competitiveness. Small and medium-sized enterprises (SMEs) will enjoy a 50% reduction in the fee for marketing authorization, down from earlier proposals as high as 95%.

Analysis

While the discovery of new drug substances will continue to feature a high proportion of traditional 'synthetic, small organic molecules', the discovery pipeline has gradually altered so as to accommodate biotechnology-derived therapeutics. In parallel with this paradigm shift, a nascent field of advanced therapies has emerged based on gene therapy, somatic cell therapy, and tissue-engineering. Each of the former has been defined in Annex I to Directive 2001/83, but tissue-engineering has lacked the same status, not least because complex combination products containing viable cells or tissues as part of a medical device were not covered by Medical Devices Directive 93/42. The Regulation was urgently required in order to remove this deficit, and to provide an integrated legal basis for the pharmacovigilance of novel and complex products based on cells and/or tissues. Only through such a centralized effort could the community ensure the free movement of these therapies and the successful operation of the internal market within this important sector.

Depending on product type, a transitional period of at least 3 years will apply for conformity of products already marketed. As for standard medicinal products, clinical trials on advanced therapies must conform to the requirements of Clinical Trials Directive 2001/20.

The Regulation distinguishes between those cells or tissues which are autologous (emanating from the patient him/herself) and allogeneic (sourced from another human being). It also provides for combinations/constructs/scaffolds based on human *or* animal origin TEP, being those which can potentially 'regenerate, repair, or replace' human cells or tissues and which, when manipulated via a manufacturing process [so that] their normal biological characteristics, physiological functions, or structural properties are substantially altered. Indeed, the cells or tissues are not intended to express the same functionality in the recipient as in the donor.

One sensible exception is that prescribed, advanced therapy medicinal products, provided in the same Member State on a customized, once-off basis for a hospitalized patient are excluded from the Regulation, while not undermining the relevant Community rules relating to quality and safety.

Practical significance

It was accepted that neither medicinal products nor medical device legislation adequately covered this emerging field. The IP professional will note the incentives available especially for SMEs; these are similar to existing 8+2+1 pharmaceutical provisions for data protection relating to pre-clinical tests and clinical trials. In parallel is the additional incentive of possible orphan 10 year market exclusivity status and the probability that a high proportion of these therapies will be deemed appropriately innovative so as to qualify for faster track approval with a consequent enlarged window for market access prior to expiry of monopoly status. Scientific advice will also be available from the EMEA at low cost and the Agency, in running a centralized procedure, will present a single interface to applicants, thus facilitating more efficient communication with the regulator and ensuring the adequacy and consistency of risk management strategies and post marketing surveillance.

While significant portions of the human genome have been patented to date, this Regulation may crystallize issues associated with ownership of cells and tissues. An Impact Assessment prepared by the Commission referred to an opinion in a staff working document that 'the file to be completed in order to obtain a patent should always include a proof of the informed consent of the donor'. This view seems outside the scope of current patent legislation.

As outlined in Human Tissues and Cells Directive 2004/23, 'human tissue and cell based products should be founded on the philosophy of voluntary and unpaid donation, anonymity of both donor and recipient, altruism of the donor and solidarity between donor and recipient'. These noble aspirations tended to be non-existent during many post-mortem practices in earlier decades.

In general, patients must have the right to know of the origin(s) of cells and tissues. With this and long-term patient safety in mind, the CAT will need to define the architecture of an adequate traceability system. The timeframe being given effect, in which this Regulation is going to overlap with Directive 2002/98 as regards human blood cells and Directive 2006/86, which will implement 'Tissues and Cells' Directive 2004/23 in respect of national measures for donor and product traceability and coding, should be in place by September 2008, may not prove adequate. Data must however be retained for a period of at least 30 years after the expiry date of the product. Should the authorization holder cease to trade following bankruptcy or liquidation, the data will come under the aegis of the EMEA.

Controversy was generated during the Parliament debate with regard to the wishes of an alliance of conservative-green members to introduce ethical amendments to exclude human embryonic and germ cells from the regulation. These were rejected and a compromise was reached (carried by 403 to 246 members): Member States will retain the right to prohibit certain products from their national markets, thus effectively retaining national sovereignty over treatments based on human embryonic stem (hES) cells. This challenges the notion of both the centralized nature of the marketing authorization application process and the equality of access for patients to products not prohibited in another Member State.

The relevant rule Article 28(2) is wide, referring to '*any* specific type of human or animal cell'. This wording may detract from the ethical possibility of trans-species or types of xenotransplantation products being foisted on a reluctant national market, but it surely also covers the previously non-controversial adult stem cells?

As passed, the Regulation seeks to ensure adequate safety and efficacy while adopting the principle of subsidiarity in attempting to avoid having to take a position on the ethical acceptability of hES or animal-derived products: the Maltese delegation to the Council has made a declaration (12 October 2007) that 'medicinal products that contain or are derived from human embryonic and foetal cells, primordial germ cells or cells derived from those cells should not have been included within the scope of the Advanced Therapy Regulation'.

Ordre public aspects of patenting inventions involving human stem cells also featured in deliberations including the Council of Europe's Convention on Human Rights

and Biomedicine (Oviedo, 1997), the United Nations Universal Declaration on the Human Genome and Human Rights (1998) and the 1995 Trade Related Aspects of Intellectual Property Rights (TRIPs) Agreement. Article 5(1) of Biotechnology Directive 98/44 confirms that 'the human body, at various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions' while juxtaposed, Article 5(2) facilitates the ability to secure a patent for an element or gene sequence isolated from the human body or otherwise produced by means of a technical process even if its 'structure is identical to that of a natural element'. Meanwhile, even though Article 6 renders unpatentable, a variety of actions based on varying the genetic identity of human beings (cloning processes) and excludes 'uses of human embryos for industrial or commercial purposes' from patenting (2(c)), in their recent book, *Contemporary Intellectual Property, Law and Policy* (OUP, 2007), MacQueen, Waelde and Laurie point out (p. 501) that it is unclear whether such prohibitions apply to *cells* derived from embryos and to cloning for the objective of producing stem cells for therapeutic purposes and not clones per se.

Such genetic interventions and the use of human embryos to produce embryonic stem cells with consequent embryo destruction will always be divisive. On the other hand, notwithstanding the confused political landscape regarding diverse national positions on funding, permitting, restricting, or prohibiting hES research, science may yet extract itself from this ethical morass if recent advances, concerning the derivation of multi-potential stem cells from non-embryo sources, in *these* cases amniotic fluid (DeCoppi, P. *et al. Nat. Biotechnol.* 25, 100–106; 2007) and reprogrammed mature mouse cells (Yamanaka, S. *et al. Cell* 126, 663–676; 2006), are validated (both Yamanaka and fellow stem-cell researcher Thomson reported further developments with reprogrammed human adult cells at the end of 2007).

Fulfilling the requirements of a highly specialized market, applicants for these *single* advanced therapy marketing authorizations will welcome this new founding legislative framework. It will not be seen as a burden. Thanks to the consistency and clarity of the legal approach based on the use of a centralized regulation, research in this fast-moving field should be stimulated in the EU; patients of diseases such as cancer, Alzheimer's and muscular dystrophy, and those victims of burns requiring skin grafts are likely to benefit from imminent yet potentially controversial treatments.

Following translation into all official EU languages and formal adoption by the Council (without further discussion), publication in the Official Journal occurred on 10 December 2007. The Regulation entered into force 20 days later and will apply 1 year after entry into force. An implementation plan has been agreed with the EMEA and on 9 January 2008 the Commission initiated the process of seeking appointees to represent clinicians and patients' associations at the CAT.

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