Cell Therapy - Current Regulatory Framework

Introduction

Cell therapy consists of the prevention or treatment of human diseases by the administration of viable cells which have been selected, cultured, often multiplied, and possibly pharmacologically treated or altered outside the body (ex-vivo) \(^1\). Cell therapy is used to replace, repair or enhance the function of damaged tissues or organs, and is part of a broader category of treatments called tissue engineering. Cell therapy has evolved since the 1930’s when it was first used by Dr. Niehans in Switzerland. Dr. Niehans used successfully a suspension of parathyroid gland cells to treat a patient with tetanus following thyroidectomy with damage to parathyroid glands. Current widely-known applications of cell therapy include the treatment of skin ulcers by skin implants manufactured in vitro from keratinocytes, knee cartilage replacement by in vitro cultured chondrocytes, and administration of hematopoietic stem cells, primarily to counteract myelodepletion and reconstitute hematopoiesis. Future applications may include treatment of Alzheimer’s disease, Parkinson's disease, other disease of the nervous system, immunotherapy, heart disease and treatment of cancer.

The type of cell used for therapy, the ex-vivo manipulation process, as well as the ultimate intended use of the cell therapy product are important for regulatory purposes, as a cell therapy product can be regulated as a drug, a device, a biological product, or a transplant. The regulatory status of a cell therapy product may vary depending on whether the cells used are autologous, allogenic, or xenogenic, or whether they are used with a synthetic biomaterial, or an encapsulation device for example. If the cells are genetically modified they are in general considered a gene
therapy product. In addition, new challenges are brought to the regulatory agencies by the emerging research conducted on human stem cells, including embryonic stem cells, embryonic germ cells, fetal stem cells, and adult stem cells. The use of some of these cells generates a number of controversial discussions, mainly because of ethical reasons \(^{(1a)}\).

As of today, there is no centralized European regulation for human engineered tissues, including cell therapy products. This article will present the wide array of different approaches present today in Europe for the regulation of cell therapy products and envision how cell therapy products could be regulated in the near future.

**Centralized approach at the EMEA**

In Europe, on a centralized basis, the European Agency for the Evaluation of Medicinal Products (EMEA) has issued guidance documents, one on the quality of human cell therapy products\(^{(2)}\), and a concept paper on xenogenic cell therapy\(^{(3)}\). This concept paper recommends that the applicants address issues such as quality, requirements for preclinical testing, requirements for clinical evaluation, and public health issues related to xenogenic cell therapy.

As compared to the situation in the USA, Europe stands at an earlier stage in terms of regulations for engineered tissue products. In the USA, engineered human tissues intended for medical use are classified according to the following three criteria\(^{(4,5)}\) - 1 - the relationship between the donor and the recipient of the biological material used to produce the tissue product, - 2 - the degree of *ex-vivo* manipulation of the cells comprising the tissue product, - 3 - whether the tissue product is intended for a
homologous use, for metabolic or structural purposes, or to be combined with a
device, drug or biologic. They have been regulated relatively successfully either as a
medical device by the Center for Devices and Radiological Health (CDRH) or as a
biologic by its Center for Biologics Evaluation and Research (CBER). A few cell
therapy products have already obtained marketing authorization such as Apligraf®
(allogenic engineered keratinocytes for the treatment of diabetic ulcers and venous leg
ulcers) and Carticel® (autologous cultured chondrocyte transplantation for the
treatment of cartilage defects of the femoral condyle).

Decentralized Approach in the Member States

As there are no centralized regulations for the control of quality, safety, and efficacy
of cell therapy products, each member state in Europe has developed its own approach
for autologous and xenogenic cell therapy products. To date, no xenogenic cell
therapy product has been authorized in Europe.

Sweden has become the only member state to decide on a firm classification of the
product as a pharmaceutical, thus clarifying regulations for a product that remains a
“gray area” in most other European countries. At the other end of the spectrum,
member states such as the United Kingdom, Ireland and Denmark have indicated
that tissue-based products are outside the scope of either pharmaceutical and medical
device legislation and hence “un-regulatable”.

Between these two extremes, member states employ a myriad of national regulations,
with no harmonization between them. The following section summarizes the current
regulatory position in some member states:
Spain

Spain regulates cell therapy products as transplants, and requires that a Tissue Bank be legally responsible for the product in Spain. The Tissue Bank is also in charge of communication with the national authorities. The Tissue Bank does not physically test material, but is informed of every single implantation or application of the product, in order to be able to inform the national authorities. No agency per se regulates the marketing of this type of product. Marketing in Spain is related to introduction to the medical centers who, themselves, are currently working with Tissue Banks, and for which a custom-developed system is in place.

Germany

In Germany, cell therapy products are classified as “unfinished drugs” and therefore not subject to submissions to the central regulatory authority, the BfArM. Instead, a company must conform to the concepts of the German Drug Law (including Good Manufacturing Products and import licenses), whilst individual Länder (regional authorities) within Germany exert local restrictions which can be as disparate as the overall European situation. In practice, a GMP certificate may suffice to demonstrate the quality of the product and to be able to market a cell therapy product in Germany.

France

In France, regulations are partially in place for cell therapy clinical trials but are not yet published for marketing authorizations. Detailed decrees of application should be
issued before the end of 2001, and are expected to clarify the situation. Allogenic cells will most likely be regulated as medicinal products, and marketed following a format similar to current marketing authorization applications (MAA). Autologous cells will be regulated on the basis of a submission describing the facility and the “process-product” as a global entity. The French medicinal agency will most likely regulate these product, not the transplant organization (Etablissement Français des Greffes).

Belgium

In Belgium, the government is actively working on regulating autologous cell therapy products. The Belgian regulation will most likely be very close to the Spanish regulations, the cells will be regulated as transplants and Tissue Banks will be responsible for such therapies on the Belgium territory and for obtaining the import/export authorizations.

Italy

In Italy, the situation is on stand-by at the moment. No regulations are in place, and there is no indication as to when they will be published. A detailed guideline on tissue engineering and cell therapy has been published by the Istituto Superiore di Sanità\(^6\), however it has not come into force. This guideline recommends that cell therapy processes be regulated as pharmaceutical products if the cell manufacturing process involved is industrial and recommends that production facilities receive accreditation from the Ministry of Health (Ministero della Sanità).
Overall, cell therapy regulations in Europe are very disparate. The situation is similar for human tissues in general (organs, tissues and cells) as demonstrated by the results of the survey conducted by the Dutch National Institute of Public Health and the Environment (RIVM\(^7\)). This document gives an extensive list of regulatory documents on organs, tissues and cells, which were provided by health authorities responding to the survey, in Europe, USA and Japan, as well as documents written by professional organizations. Based on this preliminary survey, VRIM concluded that many countries do not require a formal product review before human material is used. Also, while organs are well regulated, most countries did not appear to have any documents dealing with the requirements regarding the quality-related aspects of tissue engineered products and cells. Lastly, products may be marketed freely in some countries in absence of applicable legislation.

**Future European Regulations**

At this point there does not seem to be any difference in regulations in Europe depending on the nature of the cell therapy products, i.e. whether they are autologous, allogenic or xenogenic. One could expect that different requirements would evolve from the future regulations for all three types of tissues.

The EMEA will eventually regulate human tissues and in particular cell therapy, to fill the current void. It is expected that these products will be regulated as pharmaceutical products, with emphasis on Quality with Good Tissue Practices\(^8\), in addition to safety and efficacy. Traceability, and quality control of the cell donor, be it for autologous or allogenic therapy, will also be important for cell therapy products, in addition to general biological products requirements. Clarification of classification
of the different human tissue products will need to be improved due to the overlap between cell therapy, gene therapy, cancer vaccines, tissue engineering and regenerative medicine.

**Conclusion**

The current lack of regulations can sometimes have a negative impact for biotechnology firms operating in Europe, who are blocked in the development of their product, or cannot market their product, as in France currently. In the USA the regulations were drafted following scientific developments. Science was the basis for these regulations. The European regulators have been able to follow science and to adapt their regulations to the needs of innovative technologies, however, in some instances political issues delay the implementation of those regulations.

The European Commission is realizing that the scientific world is moving quickly and that there is a need to be proactive in issuing the regulations for the application of human tissue technology to therapeutic and prevention purposes.

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