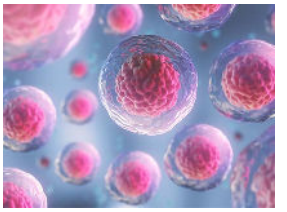

A European Regulatory Pathway for Tissue Engineering – At Last
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After many years of scientific and political struggles, the European Union now appears to be heading for success in the development of a new regulatory pathway for innovative therapeutic products, including those of tissue engineering. This article summarizes the main issues of those developments and some essentials of the proposed new regulation.

Neither drugs nor devices

I have discussed in this column before the disparate way in which the products and processes of tissue engineering are regulated in different parts of the world. The marked difference between the United States (US) and the European Union (EU) has been of particular significance. In the US, the Food and Drugs Administration has anticipated the need for new regulatory pathways that are able to deal with products that are different from conventional medical devices and pharmaceuticals. Accordingly, it has set up new procedures for so-called "Biologics" and "Combination Products" that encompass the area of tissue engineering. Conversely, the EU has had some difficulty here and there are still only the two primary pan-European routes to the market place for medical products across the EU: via the Medicinal Products Directive or the medical device Directives. For any new, innovative product that does not readily qualify as a medicinal product or as a medical device, manufacturers have to apply to each Member State for market approval. It is fortunate that significant progress has now been made towards a new regulatory procedure for these types of product, although not without some serious delays and difficulties.

It is worth remembering here the two distinct routes that medical products are regulated by in Europe. First, the Medicinal Products Directive is concerned with authorization for pharmaceuticals based on safety and efficacy, which are evaluated centrally through the European Medicines Agency (EMEA), and the procedures incorporate the well-known phases of clinical trials. Second, the medical device Directives were derived under the single market approach and the need for harmonization of the marketing of products across Europe; they involve the acquisition of a CE mark on proving compliance with the essential requirements of the Directives.

The beginning of new Directives

The EU has never had any regulatory process to deal with products used in the treatment of patients that could not be reasonably classified as either a device or as a drug. For many years the European Commission has been considering one or more new procedures to remedy this situation. The Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) of DG Sanco advised DG Enterprise in 2001 that a new procedure for tissue engineering products and processes was urgently required. It advised that neither of the existing procedures for drugs and devices would be appropriate. Its Opinion provided

a risk assessment approach to tissue engineering and identified how a new regulatory process should be able to identify and manage, as far as possible, the risks to patients associated with tissue engineering.[1]

The European Commission then took a little while to resolve some political issues concerned with the development of a new procedure and decided to tackle this in two separate ways. The first of these was concerned solely with the processes of handling human cells, which are obviously central to any tissue engineering process, but also relevant to a number of related cell therapies. This resulted in a new Directive, which was adopted in 2004.[2] This specifies standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications. It did not address the provision of products and processes and it was anticipated that a different Directive would cover these matters. However, the proposal for that second Directive was dropped in favor of a proposal for a Regulation, and the European Commission published a Consultation Paper in 2005: "Human Tissue Engineering and Beyond." This discussed a proposal for a Regulation on "Advanced Therapy Medicinal Products." These products, being gene therapy, somatic cell therapy or tissue engineered products, were defined as medicinal products. This proposal made it clear that these products were considered to be more similar to pharmaceuticals than medical devices. A clear concern expressed in the SCMPMD Opinion was that tissue engineering products should not be regulated via the CE mark procedure. This was, therefore, accommodated, but the price to pay for this was that these advanced therapy products would be regulated in a similar manner to drugs in a process that would be controlled through EMEA.

The Parliamentary debate

I believe it was widely accepted that, although some substantial scientific issues would have to be resolved if tissue engineering products were to be regulated by a variation of a drug regime, this position was much better than no position at all. However, it was at this point that much more serious problems arose to do with ethical concerns. Obviously, because these products are based on human or animal genes, cells and tissues they raise important ethical questions. The position of the European Commission was that any authorizations granted under the Regulation "should fully respect and be without prejudice to national legislations on ethics." This then indicated that individual countries could prohibit the use of certain products or technologies, for example, those based on embryonic stem cells, after recognizing that these ethical aspects are better addressed at national level.

However, some Members of the European Parliament (MEPs), including the rapporteur of the Environment Committee charged with debating and reporting on the proposal to the European Parliament, sought to promote a highly conservative line on those ethical aspects. They wanted to prohibit marketing authorizations for products that are derived from ethically controversial technologies. The first attempt from that group to introduce conservative amendments was rejected in September 2006; but a number of other MEPs re-tabled conservative amendments on ethics. A series of amendments were then discussed on 22 January 2007 in the Environment Committee, a vote took place on 30 January 2007, and a plenary vote involving the whole Parliament was scheduled to take place in March 2007.

There was then a major concern that if the European Parliament adopted the conservative amendments it would block the legislative procedure because the European Commission and the European Council Ministers would not agree. At this point, some significant lobbying took place, primarily from patient support groups and the clinical/research community. The European Parliament, the Council and the Commission tried to find a compromise package and the vote in the Parliament was postponed. The group of objecting

MEPs, however, continued with the arguments about ethics. In particular, those concerning the so-called "commercialization of the human body," wherein it was argued that no one should profit from handling human tissues. The negotiations were stopped. The proposal was eventually put to the European Parliament for its first reading on 25 April 2007. The unique outcome was that the proposal was approved in spite of the objections of the rapporteur of the Environment Committee. The proposal was then approved unanimously by the Council of Ministers on 31 May 2007 and it will now proceed on the logistical pathway to become law in 2008.

The Regulation

It does now appear that a new regulatory pathway for tissue engineering products will be in place shortly.[3] Subject to the possibility of individual ethical objections within any specific country, advanced therapy products may be marketed across Europe under a single, unified evaluation process. A tissue engineered product is defined in the Regulation as:

> "a product that 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."

It is considered that this type of product may contain cells or tissues of human or animal origin and may also contain additional substances such as cellular products, biomolecules, biomaterials, chemical substances, scaffolds or matrices. The Regulations also states that "cells or tissues shall be considered 'engineered' if they have been subject to substantial manipulation so that their original biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement, are altered." It is clear that there are going to be some difficulties and controversies over these definitions and the precise scope of the Regulation. From the materials perspective, it is interesting to note the use of the words biomaterials, scaffolds and matrices without any reference to the definitions of these terms in the context of tissue engineering. As argued before in this column, we cannot use the same criteria for biocompatibility or biological safety for both medical devices and tissue engineering products, but it hard to see how critical differences here will be addressed by the Regulation. Of even greater significance is the fact that the Regulation does not differentiate between a tissue engineered product and a process. As the science of tissue engineering develops, these critical issues will have to be considered. For now, however, it is extremely important that the Regulation has passed its difficult Parliamentary test.

References

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