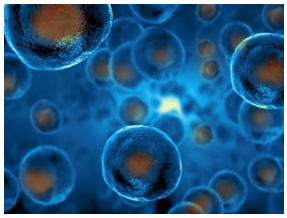

Medical Devices of Human Origin
Medical Device Technology
Material Matters, 2001

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The introduction of the concepts of tissue engineering into medical practice especially those involving human cellular and tissue-based products has necessitated a reappraisal of some of the principles of manufacturing and quality control. This article addresses some of these issues.

Tissues and devices

The manufacture of conventional medical devices is a highly regulated process, for obvious reasons. Medical device performance is as much dependent on the quality of manufacture as on the design and the materials. However, as important as quality manufacturing is, it rarely presents real difficulties because the parameters and responsibilities of manufacturing are well understood when engineering techniques and engineering materials are used.

Much attention has recently been focused on the use of tissues in the construction of medical devices and health-care products. and several new factors have emerged that must be taken into account in risk analysis and risk management. Not surprisingly, some of these concern the manufacture of these types of products. It is one thing to fabricate an article from a piece of stainless steel or polyethylene: it is quite another to carry out this process using a piece of a tissue or organ derived from an animal. Factors such as the inherent biological variability in the source material, sterility and antigenicity and shelf- life have to be addressed. Obviously these are not insurmountable problems, and many devices such as the bioprosthetic heart valves derived from pigs are common- place and generally regarded as safe and efficacious.

However. this situation has taken on new dimensions as the trend has continued, particularly because products have been developed that incorporate viable, that is, living components rather than dead tissue. They may also involve the addition of biologically active molecules that control the performance of the product. Of particular relevance is the development of products that are based on human rather than animal sources. Not long ago, doctors had available to them a series of well-defined products and processes for treating their patients, which were neatly categorized into pharmaceuticals, medical devices and transplanted tissues. Now the boundaries between these categories have changed and become blurred. We have devices that incorporate drugs and drugs that require devices for their delivery. We have devices that look more like transplants and we are moving towards products that incorporate living human cells, biologically or pharmacologically active substances and synthetic device-like structures, within the area that has come to be known as tissue engineering. How to regulate these products and how to specify, control and inspect their manufacture have become major and urgent issues.

Good Tissue Practice

In January 2001, the Food and Drug Administration (FDA) issued its proposals to deal with some of these factors.[1] It is in the process of developing a comprehensive new system for regulating human cellular and tissue-based products, and it is useful to consider some of the points raised in these proposals. A human cellular or tissue-based product is defined as a product containing or

consisting of human cells or tissues that is intended for implantation, transplantation, infusion or transfer into a human recipient. Examples of these products include cadaveric ligaments, skin, bone, dura mater, heart valves, corneas, blood hematopoietic stem cells, manipulated autologous chondrocytes and spermatozoa. It may not be intuitively obvious how these products relate to medical device technology, or why they should be of concern or interest to manufacturers of conventional medical devices. However, the rapid expansion of the whole area of tissue engineering suggests that we should all be aware of the impact that these developments will have on any sector that is involved with the technology of reconstructing the body.

FDA is proposing to regulate certain of these human cellular and tissue-based products in a different way to drugs and devices. It proposes to use Section 36l of the Public Health Service Act, which allows FDA to enforce regulations that are necessary to prevent the introduction, transmission or spread of communicable diseases, the purpose being to protect public health whilst permitting significant innovation. In essence, principles of good manufacturing practice will be supplemented by the principle of "good tissue practice." In this context, all human cells and tissues used to treat patients are referred to as "products" and persons who recover, screen, test, process, store, label, package or distribute these products are considered to be "manufacturers." The process is likely to be complicated because the products will vary considerably in their nature and in the level of risk associated with their use. A tiered, risk-based approach will lead to a system in which products that involve minimal manipulation of cells and tissue will be regulated solely under the procedures for Current Good Tissue Practice (CGTP). and those that are more than minimally manipulated will be subject to appropriate drug or device regulatory approval as well as being governed by the core requirements of CGTP

Tissue-engineered products

A few examples of the differences between processes of standard medical technology and tissue engineering should assist in understanding the need for regulated Good Tissue Practice. A typical tissue engineering product of the future may consist of some synthetic material or structure that acts as a supporting matrix or bioreactor; a culture of cells that are intended to generate new tissue; and a quantity of one or more biologically active agents that assist the cells in their prescribed function. A product of conventional technology will be based on synthetic or processed materials, usually polymers or metals. The source of these materials will normally be a vendor who is able to supply a product to meet a declared specification, for which the reproducibility is assured through adherence to these specifications and proper inspections. The performance of these materials should not vary, either from source to source or as a function of time.

Human-derived or, indeed. animal-derived cells or tissues cannot claim the same conformity to specification. Inherent biological variability means that consistency and reproducibility cannot be achieved so readily, which implies the need for greater levels of quality control over source materials. The influence of time is even more significant. Medical devices have shelf-lives, but these largely relate to the maintenance of sterility rather than any time-dependent changes in the characteristics of the device on storage. A product that incorporates living components or substances derived from tissues that were living at some time will inevitably change its characteristics with time, through the intended regeneration process or some ageing or destructive process. These processes will markedly impact on storage conditions, shelf-life, transport and other manufacturing stages.

Of even greater significance, of course, is the question of contamination. Conventional devices carry risks of infection through contamination, but sourcing components from living or recently dead donors carries much greater risks, especially in relation to viruses. Moreover, risk management related to contamination of medical devices is achieved through sterilization, which self-evidently cannot be used in products that contain viable cells and/or tissues. FDA is clearly concerned about these risks, which explains its emphasis on quality standards and process requirements that are being put in place for the manufacture of products that must be viable and sterile. FDA quotes a study related to the incidence of

infection in bone allografts.[2] Of 283 patients who had received allografts, 33 (11.7%) became infected. The outcome for these 33 patients was poor compared with the 250 uninfected patients, the majority leading to amputation or resection of the graft. Sources of contamination were considered to be related to donor infection and processing.

The use of stem cells has to be considered in this context, and clearly this is a subject that has been creating enormous interest. Cord-blood-derived stem cells are being used in place of bone-marrow transplants. These stem cells are classed as "products" and this entails a manufacturing process. Of particular importance is the fact that these products can become contaminated during collection and processing, which is exacerbated by the immunosuppressed status of many of the recipients. Among the risk factors that have emerged are the intrinsic toxicity of the cryopreservation fluids and the maintenance of sterility in the apheresis catheter throughout the delivery process. The failure to maintain sterility in these products has already been shown to pose significant life-threatening risks to these patients.

Clearly we are moving at a rapid pace into an interesting and rewarding area. It is absolutely necessary to ensure that the features of the new Good Tissue Practice are sufficiently robust to ensure that the patients derive maximum benefit from these new medical technologies.

References

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