The FDA "reinvents" human cell and tissue regulations

The US Food and Drug Adminstration (FDA; Rockville, MD) recently announced a plan to "reinvent" the regulatory framework for products derived from human cells and tissues, the sixth such program since 1993. Meanwhile, the Ministry of Health in Japan interpreted a recent World Health Organization (WHO; Geneva) recommendation on human tissue regulation as meaning it can ban certain imported tissue products.

The scope and reach of the FDA's proposed regulations, to be phased in over a few years, fall into four tiers:

First, there will be no regulations for autologous cells and tissues—those taken from a patient and transplanted into the same patient in a single surgical procedure.

Second, oversight of sample handling and infectivity only is needed for "conventional" and reproductive tissues that are minimally processed and used for their usual functions. Regulatory submissions will be limited to registration, listing, and reporting of adverse events.

The third tier is that "good tissue practices" will be required for allogeneic tissue and cells—those transplanted from one person to another. This will necessitate donor screening and testing tissues for infectious agents.

Finally, full clinical trials will only be necessary when processing of tissues and cells changes their biological or functional characteristics or when they are used for other than their normal functions. Cells used to adjust metabolism (like pancreatic islet cells), or those in some stem cell therapies, in all somatic cell therapies, and in gene therapies, are included here. Premarket approval by the FDA will be required to show safety and effectiveness because "relatively few such products have an established history of safe use," say the guidelines.

However, cells that are selected—enriched stem cells separated from lymphocytes and mature cells, for instance—will now be considered "minimally manipulated."

The new heirarchy will replace what the FDA admits have been "highly fragmented" regulations. "The agency has not previously clearly defined criteria for product characterization, sometimes resulting in confusion on the part of both industry and FDA reviewers," FDA officials say.

The product that revealed the holes in the FDA's regulatory patchwork was Genzyme Tissue Repair's (Cambridge, MA) Carticel, an autologous cell transplantation therapy placed on the market in 1995. In this system, a patient's own cartilage-producing chondrocytes are cultured in vitro and returned to the knee joint. Carticel was originally considered an unregulated medical device and reviewed by the FDA's Center for Devices and Radiological Health (CDRH). Then the FDA's division responsible for biological agents, CBER, decided the product should be considered a biologic, and that Genzyme, therefore, need to file a BLA (Biologics License Application).

Despite this intra-agency disagreement—or perhaps because of it—the FDA did not ask Genzyme to withdraw Carticel from the market. The in vitro manipulation of the cells means that, under the new regulations, Carticel falls within the FDA's second tier and is therefore now regulated.

The regulation of Organogenesis' (Canton, MA) manipulated human skin product used for wound healing, Apligraft, is unchanged under the new rules, says spokesperson Carol Hausner. Produced by separating and culturing keratinocytes and fibroblasts from discarded infant human foreskin, Apligraft contains no synthetic components, but is highly manipulated. It is currently under review as a medical device.

In contrast, heart valves and dura mater (the protective layer of tissue above the brain and below the skull) will be deregulated and considered "banked human tissue," according to the new guidelines. That pleases Biodynamics International (Tampa, FL), whose dura mater product, Tutoplast Neurosurgical Allograft, comes from human cadavers. "We would have thought the product would be upregulated," says spokesperson Robert Sicignano. The company will not change its manufacturing process from its good manufacturing practise operating procedure, although it could, he adds.

However, in late March, the Japanese Ministry of Health banned all uses of human dura mater, including Biodynamics' product, in response to a recommendation from WHO. Sicignano expects this to affect revenues significantly. "The Japanese ban. . .is a move against imports," says Sicignano. The company is lodging a strong protest with WHO against the ban, asking that its statement be revised to reflect the record of safety of their human dura mater, and requesting reinstatement of Tutoplast.

Vicki Brower