FDA seeks "comfort factors" before removing hold on porcine xenotransplantation trials

Despite the seeming precision of draft federal guidelines, officials of the US Food and Drug Administration (FDA; Rockville, MD) are seeking somewhat more nebulous "comfort factors" before removing the current "hold" on several experimental xenotransplant procedures involving pig cells and tissues. Virologists and immunologists gathered together to discuss the issues surrounding experimental xenotransplant procedures at the FDA-sponsored conference "Developing US Public Health Service Policy in Xenotransplantation," held in January at the US NIH (Bethesda, MD). Although some experts called for a general moratorium on such trials, FDA officials said they are not considering such a measure.

The current halt on porcine xenotransplantation is frustrating some researchers, including those at several companies developing potentially lifesaving xenotransplant-based technologies. However, other researchers and public-health officials say that the slowdown is prudent while risks to humans from recently recognized pig retroviruses are being evaluated. Several schemes for using pig or other nonhuman mammalian cells and tissues are under active investigation.

Virological parameters and ethical concerns had already started to move xenotransplant research away from nonhuman primates such as baboons and towards pigs. Although human immune responses quickly and almost violently reject unmodified pig tissues, a medley of genetic engineering tricks as well as the use of immunosuppressors and growth factors have provided "exciting results," indicating that at least some of those catastrophic immune system–based obstacles can be overcome, says David Sachs of the Massachusetts General Hospital (MGH; Boston, MA). "The immunology of xenotransplants is difficult, but there is no insurmountable barrier so far," he notes.

Indeed, several phase I clinical trials involving specialized pig cells indicate favorable safety profiles, and some hint at short-term efficacy in treating patients with central nervous system disorders, diabetes, and liver failure (see Table). In several cases, the pig cells are separated from human tissues by semiporous membranes or capsules. However, despite the promising safety results and the use of a range of precautionary technologies, FDA officials instituted a broad "hold" on these and other clinical trials last fall after they learned about previously unrecognized retroviruses being disseminated widely in pigs and being capable of infecting human cells in vitro (*Nature* **389**:681–682, 1997).

The primary focus of health concerns is not the xenotransplant recipients themselves, but those in contact with the recipients. The contacts face an unknown risk with no clinical benefit if porcine retroviruses jump species and cause diseases in xenotransplant recipients and their contacts. "Retroviruses can cause persistent infections and may move silently through the population," says Walid Heneine of the US Centers for Disease Control and Prevention (Atlanta GA). Others think the hazards are remote. "The risk of infection with porcine endogenous retroviruses is difficult to evaluate," says John Coffin of Tufts University Medical School (Boston, MA), summarizing discussions from an FDA-sponsored workshop held in mid 1997. "But those risks should not stop the development of xenotransplantations."

Late in 1997, an expert committee that advises FDA officials on such matters reached similar conclusions, according to Hugh Auchincloss Jr. of MGH. It concluded that pig and other xenotransplants could proceed, provided there is extensive monitoring of patients. He says, "The danger to public health is remote, and the only way to determine safety is through human trials."

"This is an enormously complex and subtle subject," says FDA Lead Deputy [Acting] Commissioner Michael Friedman. Although a group of leading university-based xenotransplant researchers is calling for a broad moratorium, he says that FDA has "no hidden agenda" and contemplates "no moratorium on all trials. . .no unanticipated regulatory action." He, other agency officials, and outside experts at the meeting preferred to speak about accumulating "comfort factors" before allowing porcine xenotransplant clinical trials to move forward, bureau-speak for defining how free of infectious agents tissues and organs must be for use in xenotranplant procedures.

The current hold on porcine clinical trials amounts to a moratorium for companies like Circe Biomedical (Lexington, MA). Circe is trying to treat liver failure by circulating patients' blood through beds containing encapsulated pig liver cells, according to company president Laszlo Eger. "We've done all sorts of virologic testing, yet we're grouped with everyone else," he says. He is convinced that the extracorporeal use of encapsulated cells is inherently safer than transplanting whole organs such as kidneys or hearts. "Very few companies are going into pivotal human trials, and this delay of more than 6 months is costing us millions of dollars and affecting the lives of many patients."

Meanwhile, the FDA draft guidelines on xenotransplants do not draw explicit attention to source-species differences in contemplated uses of such materials—a question that is divisive among investigators. Some xenotransplant researchers are vehemently opposed to use of nonhuman primates on safety grounds and therefore are inclined to place all such species "off limits" for the near future. However, other researchers say that fundamental safety concerns, not species differences, are the appropriate standards for the FDA guidelines.

Jeffrey L. Fox

Pig xenotransplant clinical development

Company	Tissue/Organ	Disease	Details
Diacrin (Charlestown, MA)	fetal pig neural cells	Parkinson's and Huntington's	phase I; favorable safety profiles in few patients tested
Genzyme Tissue Repair (Cambridge, MA)	fetal pig neural cells	Parkinson's	phase I; well tolerated in 12 patients tested
Neocrin (Irvine, CA)	encapsulated pig pancreas cells	diabetes	unknown; tested on pigs and monkeys
VivoRx (Santa Monica, CA)	encapsulated pancreas cells	diabetes	phase I; apparent clinical effects/ efficacy and no toxicities
Circe Biomedical (Lexington, MA)	pig liver cells	liver failure	phase I; favorable safety profile in 42 patients since '94
Nextran. (Princeton, NJ)	whole pig livers	organ failure	phase I (limited); no retrovirus intrusion into any of the 4 patients
Immutran (Cambridge, UK)	whole pig livers, hearts,kidneys	organ failure	unknown