Blood products part of FDA xenotransplant plan

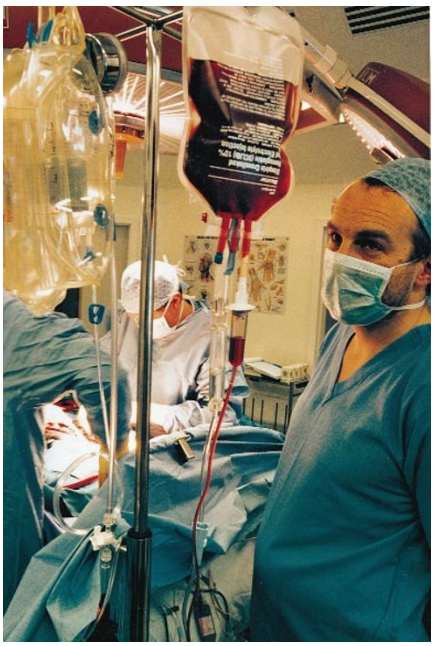
In January, US Food and Drug Administration (FDA; Rockville, MD) officials announced a broad action plan for regulating xenotransplant products and procedures—and also sought expert advice on framing principles for easing those restrictions when xenotransplantation moves from being mainly experimental to being widely used. With little practical experience at hand, however, experts appear to favor fine-tuning current precautions over developing broader principles to ease them.

Agency officials cast this exercise in principle development mainly in terms of the safety of blood and blood-derived products. In particular, they asked members of two advisory panels, other infectious disease experts, representatives from the blood product industry and from several biotechnology companies, and members of the public to review draft guidelines for safeguarding such products against becoming a source of novel pathogens that might affect the general population.

About a dozen experimental xenotransplant products and procedures are being tested clinically in the US, according to Philip Noguchi, director of the FDA Division of Cellular and Gene Therapies. "FDA is ready to put these trials on hold if there is information that is alarming regarding infectivity. We recognize that [xenotransplant procedures] are fraught with dangers."

Genzyme Tissue Repair (Cambridge, MA) already markets Epicel, its quasi-xenotransplant procedure for growing skin grafts that are used for treating about 100 patients annually who have suffered severe and extensive burn damage. Because it exposes an individual's skin to a feeder layer of irradiated mouse 3T3 cells, Epicel falls under FDA's broad rubric of xenotransplantation but is regulated as a medical device rather than as a drug or biologic.

On a voluntary basis, Genzyme Tissue Repair's scientists have subjected Epicel to extensive safety testing, with all results so far indicating that no infectious agents are transferred from the feeder layer into the human cells. FDA officials presented Epicel as a prototype for safety to the panel, but experts from several universities, including Daniel Salmon of Scripps Research Institute (La Jolla, CA) and John Coffin of Tufts University School of Medicine (Boston, MA), called for delving ever more deeply into xenotransplant-related safety questions. While they do not cast specific doubts on Epicel, their misgivings are part of a more general skepticism regarding xenotransplantation safety testing. Put simply:



The new regulations on xenotransplantation will be particularly important for blood and blood-derived products.

How can anyone be sure that any xenotransplant product or procedure does not transmit novel pathogens when they are not yet discovered and there is thus no clear method to test for them?

FDA officials and outside experts therefore generally describe the risk as "hypothetical," while also acknowledging real disasters attributable to HIV, several blood-borne viruses that cause hepatitis, and the agents that are deemed responsible for transmissible spongiform encephalopathies.

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However, agency officials also are very much aware of the near-term and very real health-related concerns that arise because of blood and blood-derived product shortages. "The risks ... of transmission are undefined, but the risk of blood products becoming unavailable are immediate," says Andrew Dayton of the FDA Division of Transfusion Transmitted Diseases. "If one donor is suspect, we can lose a significant part of the plasma supply."

Suppliers of blood and blood products are particularly frustrated with recommendations in the draft guidelines that could further complicate blood donations. "[U]nvalidated donor interrogation ... for the theoretical risks of xenotransplantation may, at worst, paradoxically increase other risks of transfusion, and at best will contract further an already shrinking donor base," says Kay Gregory of the American Association of Blood Banks (Bethesda, MD), referring to a range of questions in FDA draft guidelines for potential blood donors to address.

With such shortages in mind, members of the advisory panel suggest measures to simplify blood donor questionnaires and to circumscribe the reach of the draft precautions. For instance, they suggest simplifying the draft guidelines to put more of the burden for withholding potentially tainted blood on the small numbers of xenotransplant recipients, who should be warned during the informed-consent process, before they undergo a transplant, rather than later when they might want to donate blood. Such steps will have little practical impact on the overall blood supply because of the low numbers of individuals participating in xenotransplant clinical trials.

Panel members also recommend another change to the draft to ensure that the blood supply is maintained even while special precautions are kept in place against it becoming a source of novel pathogens. Thus, the prohibitions against donating blood should apply only to xenotransplant recipients and those other individuals, such as sex partners, who have "intimate" contact with the recipients. Meanwhile, others who have close but not intimate contact with xenotransplant recipients, such as research and medical staff or members of the same household, should continue to be permitted to donate blood.

Among the general public, the most vehement critics of xenotransplants contend that experimental xenotransplants should be slowed or stopped and that any recipients should be meticulously monitored for extended periods following such procedures. FDA is "ill-prepared to protect the public from infectious diseases that might result from animal-to-human organ, cell, and tissue transplants," maintains Alix Fano, director of the Campaign for Responsible Transplantation (New York), a coalition of public interest groups that opposes xenotransplantation. She calls for a national name-based registry of all transplant recipients and their close contacts.

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