Regulating Clinical Xenotransplantation in the United States

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The shortage of human organs available for transplantation coupled with recent advances in technology and pharmacology that have been important for achieving success in allotransplantation have led some to propose xenotransplantation, initially attempted almost 90 years ago,[1,2] as a potential solution to the human allograft shortage.[3,4] In addition, the use of nonhuman animal cells has been proposed for restoring physiological or functional deficiencies and treating chronic debilitating disorders.[5,6] Although clinical xenotransplantation may provide substantial benefits, there are biological and ethical issues that must be addressed.

Perhaps the single most serious public health concern for the clinical use of xenotransplantation is the potential for the transmission of infectious disease from nonhuman animals to human xenotransplantation recipients and then to others in the human population. Because of this potential risk to the public health, four agencies of the United States Public Health Service (PHS), together with the Office of the Assistant Secretary for Planning and Evaluation (OASPE) of the Department of Health and Human Services (DHHS), have worked to develop a xenotransplantation policy that is based on scientific evidence and public input, and is intended to minimize the infectious disease risks. The four PHS agencies include the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resource Services Administration (HRSA) and National Institutes of Health (NIH).

In 1996, the PHS published a "Draft Guideline on Infectious Disease Issues" in Xenotransplantation (Federal Register 61:49920,49932, 1996) for public comment. The Draft Guideline identified general principles for the prevention and control of infectious diseases that may be associated with xenotransplantation and that may pose a public health hazard. These principles addressed such issues as source animal selection, isolation of patients, pre- and post-transplant monitoring of patients, and informed consent and education. In response to written public input, public commentary gained at several public meetings, including a public workshop held in Bethesda, Maryland, January 21-22, 1998, entitled Developing U.S. Public Health Policy in Xenotransplantation, and advances in relevant science, the guideline has been revised. (Internet access through http://www.fda.gov/cber/xap/xap.htm).

The PHS defines xenotransplantation as "any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (A) live cells, tissues, or organs from a nonhuman animal source or (B) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs." Xenotransplantation products are defined as "live cells, tissues or organs used in xenotransplantation." A crucial part of both of these definitions is that the nonhuman cells, tissues, or organs used in xenotransplantation and in the manufacture of xenotransplantation products must be alive. Part B of the xenotransplantation definition is intended to include xenotransplantation products in which human cells, tissues or organs, having had ex vivo exposure to live animal materials, are administered to humans. Ex vivo contact is thought to pose risks for transmission of xenogeneic infectious diseases qualitatively similar to those posed by implantation of xenogeneic cells, tissues or organs. This concept was discussed by FDA advisors at two meetings of the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee

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(June 3-4, 1999; transcript available at http://www.fda.gov/ohrms/dockets/ac/cber99.htm# Biological Response Modifiers Advisory Committee; and January 13, 2000; transcript available at http://www.fda.gov/ohrms/dockets/ac/cber00.htm# Biological Response Modifiers Advisory Committee).

The revised PHS guideline also clarifies issues of clinical protocol review and oversight, responsibility for design and conduct of the clinical trials, patient informed consent, xenotransplantation product sources, source animal screening and qualification, and specimen archives and medical records. It furthermore refers to the creation of the Secretary's Advisory Committee on Xenotransplantation (SACX), which will provide a public forum for further discussions of xenotransplantation.

The revised PHS guideline reiterates that the clinical use of xenotransplantation products in the United States is regulated by the FDA by authorities of the Public Health Service Act (42 U.S.C. 262)[7] and section 201 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321).[8] The regulation of xenotransplantation products by the FDA has been discussed publicly on several occasions, including at the January 21-22, 1998, PHS public workshop mentioned above. In addition, FDA has held several meetings of the Xenotransplantation Subcommittee of its Biological Response Modifiers Advisory Committee, to discuss various emerging issues in xenotransplantation. The most recent of these meetings was held January 13, 2000.

To proceed, all clinical trials involving the use of xenotransplantation products must be conducted under FDA regulation either through an investigational new drug application (IND) for biologic products or an investigational device exemption (IDE) for certain xenotransplantation products that may be regulated as devices. These investigational phases of development of xenotransplantation products must be in compliance with 21 CFR part 312 for INDs or 21 CFR Part 812 for IDEs. All xenotransplantation products must have pre-market approval prior to commercial distribution within the United States. The type of approval required would depend upon the specific xenotransplantation product, but most will be regulated as biologics and require a Biologics License, while others may require approval as a device.

FDA has also issued guidance documents to clarify and expand on the regulation of xenotransplantation. In response to concerns articulated by scientists and members of the public regarding the use of nonhuman primates as sources of xenotransplantation products, and following consultation with other DHHS agencies, on April 6, 1999, FDA published a Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans. (Document can be accessed on the Internet through http://www.fda.gov/cber/xap/xap.htm.) This document was issued for immediate implementation. FDA concluded that "the use of nonhuman primate xenografts in humans raises substantial public health safety concerns within the scientific community and among the general public; [that] current scientific data indicates that human subjects, including individual xenotransplant recipients, their close contacts, and the public at large, would be exposed to significant infectious disease risk by the use of nonhuman primate xenografts; and [that] further scientific research and evaluation is needed in order to obtain sufficient information to adequately assess and potentially to reduce the risks posed by nonhuman primate xenotransplantation." Therefore, FDA recommended that protocols proposing the use of nonhuman primate xenotransplantation products should be discussed at public advisory committee meetings and not be submitted to FDA until sufficient information is available to assess their safety. FDA further stated that, until such time, these protocols would not be allowed to proceed.

On December 23, 1999, FDA made public a draft document entitled Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Contacts. (Document can be accessed on the Internet through http://www.fda.gov/cber/xap/xap.htm.) The document recommends indefinite deferral from blood donation for xenotransplantation product recipients and certain of their contacts. This document has been discussed at two separate FDA Advisory Committee meetings in January and March 2000, and will undergo revision based on these discussions and public commentary.

The regulation of xenotransplantation continues to evolve as information accumulates. Thus, whether regulatory policies become more liberal or more restrictive will depend upon future scientific and clinical data as well as public input. FDA will continue to update and revise its advice appropriately. In addition, the U.S. is working with appropriate officials from other countries toward international

collaboration and coordination of this important health policy area.

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