Guidance For Industry

Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans

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I. PURPOSE

This document is intended to provide guidance on nonhuman primate xenotransplantation. Xenotransplantation is defined for the purpose of this document as the use of live cells, tissues**,** or organs from a nonhuman animal source transplanted or implanted into a human, or used for ex vivo contact with human body fluids, cells, tissues**,** or organs that are subsequently given to a human recipient. For the purpose of this document, xenografts include live cells, tissues or organs from a nonhuman animal source used for xenotransplantation. This document provides guidance to industry concerning: (1) the potential public health risks posed by nonhuman primate xenografts; (2) the need for further scientific research and evaluation of these risks, particularly infectious agents; and (3) the need for public discussion concerning these issues.

II. INTRODUCTION

The agency is soliciting public comment but is implementing this guidance immediately because of the public health concerns related to the use of live cells, tissues, and organs from nonhuman primates in humans (i.e., nonhuman primate xenotransplantation).

In developing this guidance the Food and Drug Administration (FDA) considered numerous sources of information, including concerns raised in public comments to the Docket No. 96M-0311 for the "Draft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation" (61 FR 49920, September 23, 1996), and concerns voiced by the scientific and lay community at the public workshops on xenotransplantation sponsored by the Public Health Service and entitled "Cross-Species Infectivity and Pathogenesis" (July 21 and 22, 1997), and "Developing U.S. Public Health Service Policy in Xenotransplantation" (January 21 and 22, 1998).

This guidance is issued now in response to these public comments and recent interest among clinical investigators in using nonhuman primate xenografts in the near future.

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[1] This guidance document represents the agency's current thinking on the potential public health risks posed by the use of nonhuman primate xenografts in humans, and the consequent need for further scientific evaluation and public discussion of this issue. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

While this guidance addresses the issue of nonhuman primate xenotransplantation, the agency is aware that other species of animals have been used and are proposed as future sources of xenografts and may pose infectious disease risks; the public health issues raised by xenotransplantation, regardless of source animal species, have received and will continue to receive scientific evaluation and discussion by appropriate federal agencies and advisory committees. The issues raised in the Draft PHS Guideline on Infectious Disease Issues in Xenotransplantation will be addressed in a subsequent revision of the guideline that takes into consideration the public comments received and recent scientific developments; this revised document will be issued at a later date.

The approach outlined in this guidance document has been accepted by the other Public Health Service agencies including the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Health Resources and Services Administration (HRSA), as well as the Department of Health and Human Services (DHHS) Working Group on Xenotransplantation.

III. BACKGROUND

The success of clinical transplantation of human grafts to patients with organ failure has increased the demand for human cells, tissues and organs in the treatment of human disease far beyond the available supply. Despite intensified efforts to enlarge the pool of human graft donors, there is a critical shortage of human grafts available for transplant. Approximately half of patients with end-stage disease of vital organs - such as liver, heart, and kidney - die while awaiting transplantation. The unmet and growing demand for human cells, tissues, and organs coupled with recent advances in the science of immunology and molecular biology (e.g., potent immunosuppressive drugs, transgenic techniques) have stimulated interest in the transplantation of animal cells, tissues, and organs in lieu of human cells and organs.

A. Guidance and Recent Review of Guidance

The United States Public Health Service (PHS) agencies including the FDA, NIH, CDC, and HRSA have worked together to address: a) the infectious disease risks posed by xenotransplantation; b) the baseline safety measures for the procurement, screening, and use of xenografts; and c) the clinical care of xenograft recipients within the U.S. These agencies jointly published the "Draft PHS Guideline on Infectious Disease Issues in Xenotransplantation." The guideline sets forth proposed measures to reduce the risk to the public of human disease due to known and emerging infectious agents resulting from xenotransplantation. The guideline was published for public comment in the *Federal Register* of September 23, 1996 (61 FR 49920); over 140 public comments were received. Many public commentators expressed specific opposition to the use of nonhuman primate xenografts due to public health risks from transmission of infectious diseases. This opposition was voiced in a letter from 44 virologists and in other letters from: (1)

individual citizens including members of the scientific and medical communities, and representatives of the American Society of Transplant Physicians and the American College of Cardiology; and (2) commercial sponsors of xenotransplantation clinical trials.

Concerns regarding the use of nonhuman primate xenotransplantation were also expressed at the recent public workshop sponsored by the PHS and entitled "Developing U.S. Public Health Policy in Xenotransplantation" (held on January 21 and 22, 1998, in Bethesda, Maryland). The workshop was part of an ongoing series of public workshops that the PHS is sponsoring to facilitate further scientific evaluation of the potential public health risks and benefits posed by xenotransplantation and to enhance public awareness and to obtain feedback on the public health issues raised by xenotransplantation.

B. Risks Associated with Nonhuman Primate Xenotransplantation

Xenotransplantation raises a major public health dilemma: how to balance the potential promise of this emerging technology to alleviate the shortage of live cells, tissues, and organs currently available for transplantation with the risk of potential transmission of infectious agents to the patient, his/her close contacts, and the public at large. Experience with human-to-human transplantation has demonstrated the transmissibility of infectious agents from donor to recipient through transplants (e.g., Human Immunodeficiency Virus (HIV), Creutzfeldt-Jacob Disease, Hepatitis B Virus, and Hepatitis C Virus).

Many infectious diseases of animals can be transmitted to humans via routine exposure to or consumption of animals (e.g., rabies). Viruses that are not pathogenic in their natural host reservoirs may, in some cases, be highly pathogenic when transmitted to a new host species. Several zoonotic viruses have produced significant outbreaks when introduced into human hosts under normal circumstances of exposure (e.g., Ebola, Hanta Virus, Influenza).

Xenotransplantation may facilitate inter-species spread of infectious agents from animals to the human host through several mechanisms: a) surgery disrupts the normal anatomical barriers to infection such as skin, membranes, etc.; b) transplant recipients are usually iatrogenically immunosuppressed to facilitate graft survival; and c) patients' underlying disease(s), such as AIDS or diabetes, may compromise their immune response to infectious agents. Consequently, the recipient of a xenotransplant is potentially at risk for infection with infectious agents already known to be transmissible from animals to humans as well as with infectious agents which may become transmissible only through xenotransplantation and which may not be readily identified with current diagnostic tools. Infected xenograft recipients could then potentially transmit these infectious agents to their contacts and subsequently to the public at large. In this regard, infectious agents which

result in persistent latent infections which may remain dormant for long periods before causing clinically identifiable disease are of particular concern.(1)

There are anatomic, physiologic, and immunologic similarities between nonhuman primates and humans. These similarities diminish the immunologic and other functional barriers to the survival and adequate functioning of a nonhuman primate xenograft in human hosts. For these reasons, some clinical investigators have favored the use of nonhuman primates as potential sources of cells, tissues, and organs for xenotransplantation. Structural and functional similarities may also facilitate the transmission of certain infectious agents from nonhuman primate xenografts to the human host (e.g., similarities in cell surface receptors may allow entry of simian viruses into human host cells).

Additional concerns exist regarding the use of nonhuman primates as source animals for xenotransplantation. Current animal husbandry practices do not ensure adequate pathogen-free status of nonhuman primates. The recent removal (often 1 to 2 generations ago) of many nonhuman primates from the wild state increases the difficulty of adequately identifying the infectious agents potentially transmissible to humans.

Nonhuman primates harbor several known infectious agents which are potential human pathogens and which can produce clinically latent infections and/or persistent infections. These agents include a variety of retroviruses (e.g., Simian Immunodeficiency Virus [SIV], Simian Foamy Viruses [SFV], Simian T-Lymphotropic Viruses [STLV], Baboon Endogenous Retrovirus, and/or Simian Type D Retroviruses) and a variety of herpes viruses (e.g., herpesvirus papio, baboon cytomegalovirus [CMV], and SA-8). These agents are often found at high rates in nonhuman primate colonies. Most nonhuman primates harbor SFV and several studies have demonstrated that SFV from nonhuman primates can persistently infect humans occupationally exposed to these animals. (2,3,4) Human cells infected with SFV exhibit cytopathic effects; whether or not SFV can cause disease in humans and/or can be subsequently transmitted among humans is currently unknown. Cercopithecine herpesvirus 1 (or B virus) transmitted from macaques to humans can result in the rapid onset of encephalitis and death. (5) Several of the Simian Immunodeficiency Viruses (SIVs) can infect human cells in tissue culture and there has been documented infection of humans with SIVs (e.g., infection of a laboratory worker with SIVmac). (6)

Evidence suggests that transmission of certain infectious agents from nonhuman primates to humans can have serious public health consequences. For example, evolutionary studies suggest that the HIV types 1 and 2 (HIV-1 and HIV-2) have originated by cross-species infection from their simian counterparts in chimpanzee (SIVcpz) and sooty mangabey (SIVsm), respectively. (7,8)

IV. RECOMMENDATIONS

FDA has reviewed the currently available scientific information and has considered the public comments submitted to the Docket No. 96M-0311 and expressed at recent PHS-sponsored public workshops on xenotransplantation regarding the use of nonhuman primate xenotransplantation. Based on this review, and following consultation with the NIH, CDC, HRSA, and the DHHS Working Group on Xenotransplantation, the FDA has concluded that:

(1) the use of nonhuman primate xenografts in humans raises substantial public health safety concerns within the scientific community and among the general public;
(2) 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
(3) 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.

In light of these considerations, the FDA has determined the following concerning the use of nonhuman primate xenografts in FDA-regulated products intended for human use:

(1) an appropriate federal xenotransplantation advisory committee, such as a Secretary's Advisory Committee on Xenotransplantation (SACX) currently under development within the DHHS, should address novel protocols and issues raised by the use of nonhuman primate xenografts, conduct discussions, including public discussions as appropriate, and make recommendations on the questions of whether and under what conditions the use of nonhuman primate xenografts would be appropriate in the United States.
(2) clinical protocols proposing the use of nonhuman primate xenografts should not be submitted to the FDA until sufficient scientific information exists addressing the risks posed by nonhuman primate xenotransplants. Consistent with FDA Investigational New Drug (IND) regulations [21 CFR 312.42(b)(1)(iv)], any protocol submission that does not adequately address these risks is subject to clinical hold (i.e., the clinical trial may not proceed) due to insufficient information to assess the risks and/or due to unreasonable risk.
(3) at the current time, FDA believes there is not sufficient information to assess the risks posed by nonhuman primate xenotransplantation. FDA believes that it will be necessary for there to be public discussion before these issues can be adequately addressed.

V. FOOTNOTES

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(4) Heneine, W. et al., Identification of a Human Population Infected with Simian Foamy Viruses, Nature Medicine 1998;4:403-7.

(5) Weigler, B.J., Biology of B Virus in Macaque and Human Hosts: a Review. Clin Infect Dis 1992;14:555-67.

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(7) Gao, F. et al., Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. Nature 1999;397:436-441.

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