DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

[Docket No. 96M–0311]

Draft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation (August 1996)

AGENCY: Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The Public Health Service (PHS) is publishing a document entitled, ''Draft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation (August 1996).'' The demand for human cells, tissues, and organs for clinical transplantation continues to exceed the supply. Thus, the development of xenotransplantation, an investigational therapeutic approach that uses cells, tissues, and organs of animal origin (xenografts) in human recipients, has become an important area of research. The purpose of this draft guideline is to discuss public health issues related to xenotransplantation and recommend procedures to diminish the risk of transmission of infectious agents to the recipient and the general public.

DATES: Written comments December 23, 1996.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration (FDA), 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the guideline and received comments are available for public examination in the Documents Management Branch between 9 a.m. and 4 p.m., Monday through Friday. The draft guideline is set forth in this document. Submit written requests for single copies of the draft guideline to the Manufacturers Assistance and Communications Staff (HFM–42), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your request. The document may also be obtained by mail or FAX by calling the CBER FAX Information System at 1–888–CBER–FAX or 301–827–3844.

Persons with access to the INTERNET may obtain the guidance document using FTP, the World Wide Web (WWW), or bounce-back e-mail. For FTP access, connect to CBER at ''ftp://ftp.fda.gov/ CBER/''. For WWW access, connect to CBER at ''http://www.fda.gov / cber/cberftp.html''. For bounce back e-mail send a message to ''Xeno@al.cber.fda.gov''.

FOR FURTHER INFORMATION CONTACT: Timothy W. Beth, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 200 North, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION: For the purposes of this draft guideline, the germ ''xenotransplantation'' refers to any procedure that involves the use of live cells, tissues, and organs from a nonhuman animal source, transplanted or implanted into a human or used for ex vivo perfusion. These live nonhuman cells, tissues, or organs are called xenografts. Xenograft products include those from transgenic or nontransgenic animals, as well as combination products that contain xenografts in combination with drugs or devices. Xenograft products do not include nonliving animal products, many of which are regulated as devices (porcine heart valves), drugs (porcine insulin), and other biologicals (bovine serum albumin).

As with human transplantation, rejection and failure to engraft remain important medical and scientific challenges in xenotransplantation. In addition, there are concerns about potential infectious disease and public health risks. Diseases of animals can be transmitted to humans through routine exposure to, or consumption of, animals. Because transplantation bypasses most of the patient's usual protective physical and immunological barriers, transmission of known and/or unknown infectious agents to humans through xenografts may be facilitated. Moreover, infectious agents vary considerably from one to another with respect to the nature of the risks they present and the difficulty of managing those risks. For example, some agents, such as retroviruses and prions, may not produce clinically recognizable disease until many years after they enter the host, and some infectious agents are not readily detected or identified in tissue samples by current diagnostic techniques.

Despite the technical barriers and potential risks, xenotransplantation shows promise both as a treatment for a wide range of diseases including chronic metabolic and neurological disorders and as an alternative source of cells, tissues, and organs for clinical transplantation. For these reasons, academic and commercial sponsors are actively pursuing the development of xenograft products and their clinical application. The Health Resources and Services Administration (HRSA) and the Health Care Financing Administration (HCFA) within the Department of Health and Human Services (DHHS) currently administer programs overseeing human organ transplantation under the authority of the National Organ Transplant Act of 1984 (NOTA) (42 U.S.C. 273 *et seq.*, as amended). In the Federal Register of May 2, 1996 (61 FR 19722), DHHS published final rules governing performance standards for organ procurement organizations. FDA currently regulates human somatic cell therapies (see ''Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products,'' (58 FR 53248, October 14, 1993)) and human tissue for transplantation (21 CFR part 1270).

The public health safety issues raised by xenotransplantation differ from those of human transplantation in several significant ways. First, the spectrum of infectious agents transmitted via human organ transplantation has been well established, while the full spectrum of infectious agents potentially transmitted via xenograft transplantation is not well known. Infectious agents that produce minimal symptoms in animals may cause severe morbidity and mortality in humans. Second, HRSA oversight and administration of the human organ donor and recipient matching and tracking creates a system that ensures that high standards are maintained in human organ transplantation. Animals are currently commercially bred and raised as a source of food and other products; animals can also be bred and raised as sources of xenograft products for clinical transplantation. As the commercialization of xenograft production increases throughout the United States and the world, the need for consistent standards of source animal screening and quality control will grow. Third, the potentially unlimited supply of animal cells, tissues, and organs may allow opportunities for developing therapeutic approaches to a wide range of diseases for which treatments have heretofore been limited by the insufficient availability of human organs and tissues.

I. Regulation of Xenotransplantation Clinical Investigations

A number of experimental clinical investigations that use xenograft products are being carried out under FDA oversight using the investigational new drug application (IND). Examples of these clinical trials include using

fetal porcine neural cells for Parkinson's disease, encapsulated bovine adrenal cells for intractable pain, encapsulated porcine islet cells for diabetes, baboon bone marrow for AIDS and transgenic porcine livers as a temporary bridge to human organ transplantation.

The clinical investigation of drugs and biological products, including xenograft products (live animal cells, tissues, and whole organs), is subject to investigational new drug regulations in 21 CFR part 312, institutional review board regulations in 21 CFR part 56, and informed consent regulations in 21 CFR part 50. FDA plans to develop further guidance, that will be announced in the Federal Register, to assist sponsors in submitting to FDA the appropriate information to be included in an IND for clinical investigation of xenograft products.

II. Recent Events

In 1994 several Institutional Review Board (IRB) committees contacted the Centers for Disease Control and Prevention (CDC) and FDA regarding proposed solid organ xenotransplants from nontransgenic animals, and expressed concern regarding the source and characterization of donor animal tissues. Contemporaneously, the Assistant Secretary of Health requested that agencies in PHS develop a consensus on the infectious disease risks and safety issues raised by xenotransplantation. Even though there were well documented examples of trans-species infection of humans through routine animal exposure, no guidelines existed regarding the adequate screening of donor animal cells, tissues, and organs intended for human transplant or recommendations for post-transplantation patient monitoring.

To strike a balance between the public health risks and the potential promise of xenotransplantation, FDA, CDC, and the National Institutes of Health (NIH) have worked together to create a draft PHS guideline that seeks to address the concerns raised by the clinical use of xenograft products in humans. As part of the development of the guideline, FDA held an open public meeting of the Biologics Response Modifiers Advisory Committee (BRMAC) on April 21, 1995, at which elements of the draft xenotransplantation guideline and proposed clinical trials were discussed (see 60 FR 15147, March 22, 1995). Essential elements of the draft PHS guideline and a novel clinical trial to use baboon bone marrow for a patient with AIDS were also discussed at the July 13, 1995 meeting of the BRMAC (see 60 FR 32330, June 21, 1995). The PHS agencies including, FDA, CDC, NIH, and HRSA have discussed the development of the draft PHS guideline on infectious disease issues in xenotransplantation at numerous scientific meetings and public forums, and PHS scientists have authored scientific and lay reports on the subject of xenotransplantation.

FDA, CDC, NIH, and HRSA also supported a study and public workshop by the Institute of Medicine (IOM) on the scientific, public health, and ethical implications of xenotransplantation which culminated in a report released on July 17, 1996, entitled, ''Xenotransplantation: Science, Ethics, and Public Policy'' (hereinafter referred to as the IOM report). In addition to exploring some of the social, scientific, and ethical concerns associated with xenotransplantation, the IOM report also recommended that national guidelines be established for all experimenters and institutions that undertake xenotransplantation trials in humans. (Copies of the IOM report can be obtained from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, 202–334–3313 or 800–624–6242.)

III. Submission of Comments

It is the intention of PHS to revise the draft guideline based on the comments received and to issue a revised guideline at a later date. The availability of any revised guideline will be announced in the Federal Register, the *NIH Guide for Grants and Contracts,* and CDC's *Morbidity and Mortality Weekly Report.* As with other guidelines, PHS does not intend this draft guideline to be all-inclusive and cautions that not all information contained therein may be applicable to all situations. The draft guideline is intended to provide information and does not set forth requirements. The methods and procedures cited in the draft guideline are suggestions.

PHS recognizes that advances will continue in the area of xenotransplantation and that this document may require revision as those advances occur. This draft guideline does not bind PHS and does not create or confer any rights for or on any person and does not operate to bind PHS or the public. The draft guideline represents PHS's current thinking on infectious disease issues in xenotransplantation. In addition, the issuance of this draft guideline by PHS should not be construed as an endorsement of the readiness of xenotransplantation clinical trials or a commitment to direct funds to support additional basic or preclinical research in this area.

Interested persons may submit written comments regarding this draft PHS guideline at any time to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments received will be considered in any revision to the ''Draft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation (August 1996).''

The text of the draft guideline follows.

Draft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation (August 1996)

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1. Introduction

1.1. Background

The demand for human cells, tissues, and organs for clinical transplantation continues to exceed the supply. The resultant limited availability of human allografts, coupled with recent scientific and biotechnical advances, has prompted the development of new investigational therapeutic approaches that use cells, tissues, and organs of animal origin (xenografts) in human recipients. Transmission of infections (HIV/AIDS, Creutzfeldt-Jakob Disease, rabies, hepatitis B, hepatitis C, etc.) via transplanted human allografts has been well documented. The use of live

animal cells, tissues, and organs for transplantation or hemoperfusion of humans raised unique public health concerns about potential infection of the patient with both recognized and/or unknown infectious agents. Additionally, subsequent introduction of these xenogeneic infectious agents into and propagation through the general human population is a risk that must be addressed.

Zoonoses are defined as diseases of animals transmitted to humans via routine exposure to or consumption of the source animal. Many agents responsible for zoonoses are well characterized and identifiable through available diagnostic tests, e.g., Toxoplasma species, Salmonella species, or Herpes B virus of monkeys. However, public health concerns exist regarding the potential transmission of xenogeneic infectious agents not recognized as classical zoonoses from xenografts to recipients, and then from the recipient to other persons. The intimate contact between the recipient and the xenograft, the associated disruption of anatomical barriers, and immunosuppression of the recipient are more likely to facilitate interspecies transmission of xenogeneic infectious agents than normal contact between humans and animals.

Emerging infectious agents may not be readily identifiable with current techniques, as exemplified by the delay of several years in identifying HIV–1 as the pathogenic agent for AIDS. Improvement in diagnostic techniques facilitated investigation of exogenous and endogenous retroviruses in all species. Retroviruses and other persistent viral infections may be associated with acute disease with varying incubation periods, followed by periods of clinical latency prior to the onset of clinically evident malignancies or other chronic diseases. As the HIV/AIDS pandemic demonstrates, persistent viral infections may result in person to person transmission for many years before clinical disease develops in the index case, thereby allowing an emerging infectious agent to become established in the susceptible population before it is recognized.

1.2. Scope of the Document

The draft guideline discusses public health issues related to xenotransplantation and recommends procedures for diminishing the risk of transmission of infectious agents to the recipient, health care workers, and the general public. This draft guideline applies to all xenotransplantation procedures performed in the United States. For the purposes of this draft guideline, the term ''xenotransplantation'' refers to any procedure that involves the use of live cells, tissues and organs from a non-human animal source, transplanted or implanted into a human or used for ex vivo perfusion. This draft guideline reflects the status of the field of xenotransplantation and knowledge of the risk of xenogeneic infections at the time of publication. This draft guidelines will require periodic review and may require modification when justified by advances in scientific knowledge and clinical experience.

1.3. Objectives

The objective of this draft Public Health Service (PHS) guideline is to present measures that can be used to minimize the risk to the public of human disease due to known zoonoses and emerging xenogeneic infectious agents arising from xenotransplantation. In order to achieve this goal, this document:

1.3.1. Outlines the composition and function of the xenotransplant team in order that appropriate technical expertise can be applied and that adequate data management, tissue storage, and surveillance procedures can be established.

1.3.2. Discusses aspects of the clinical protocol, clinical center and the informed consent relevant to public health concerns regarding infections associated with xenotransplantation.

1.3.3. Provides a framework for pretransplantation animal source screening to minimize the potential for cross-species transmission of known and unknown zoonotic agents.

1.3.4. Recommends approaches for postxenotransplantation surveillance to monitor for the potential transmission to the recipient and health care workers of infectious agents, including unlikely or previously unrecognized agents.

1.3.5. Recommends hospital infection control practices to reduce the risk of nosocomial transmission of xenogeneic infectious agents.

1.3.6. Recommends the archiving of biologic samples, (including sera, plasma, leukocytes, and tissues), from the source animal and the transplant recipient for the potential investigation of infectious diseases arising from xenotransplantation which could impact upon the public health.

1.3.7. Recommends the creation of a centralized database. This database will address the need for long term safety data required for public health investigations.

2. Xenotransplantation Protocol Issues

2.1. Xenotransplant Team

The transplantation of animal cells, tissues, and organs requires expertise in the evaluation of infectious agents in the source animal and in the recipient. Consequently, in addition to transplant surgeons, the xenotransplantation team should include as active participants such individuals as: (1) Infectious disease physician with expertise in zoonoses, transplantation, and microbiology; (2) veterinarian with specific expertise in the animal husbandry issues and infectious diseases (particularly zoonoses) of the animal species serving as the source of transplanted cells, tissues or organs (animal source); (3) transplant immunologist; (4) hospital epidemiologist/infection control specialist; and (5) director of the clinical microbiology laboratory.

2.2. Clinical Xenotransplantation Site

All clinical centers involved with xenotransplantation should have active participation with accredited virology and microbiology laboratories that have the documented expertise and capability to isolate and identify unusual and unknown pathogens of both human and veterinary origin. Centers where solid organ xenotransplantation procedures are performed should be members of the Organ Procurement and Transplantation Network and abide by its policies in accordance with Section 1138 of the Social Security Act (42 U.S.C. 13206–13208).

2.3. Clinical Protocol Review

After completion of internal review by all members of the xenotransplant team, clinical protocols should be reviewed by the clinical center Biosafety Committee, Institutional Animal Care and Use Committee (IACUC), and Institutional Review Board (IRB). The Biosafety Committee should have the expertise to assess the potential risks of infection for contact population (including health care providers, family, friends, and the community at large) and the recipient. The IACUC should have the expertise to evaluate epidemiological concerns related to conditions of source animal husbandry (e.g., frequency of screening, animal quarantine, etc.). The IRB should have expertise in human and veterinary infectious diseases, including virology and laboratory diagnostics, epidemiology, and risk assessment. The review committees should discuss their comments and suggestions with the members of the health care team and the informed consent document should

incorporate and reflect these comments, as needed. In addition, live animal cells, tissues, and organs intended for use in humans are subject to regulation by FDA under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act (42 U.S.C. 262, 264 and 21 U.S.C. 301 *et seq.*).

2.4. Health Surveillance Plans

The clinical protocols for xenotransplantation should describe the methodologies for screening for known infectious agents before transplantation (including the herd, the individual animal and the xenograft) and surveillance after transplantation (including the recipient(s), their contacts, and the health care workers (section 4)). The agents and screening methods may vary with the different types of procedures, the cells, tissues, and organs used, and the animal source. The clinical protocol should include a summary of the relevant aspects of the health maintenance and surveillance program of the herd and the medical history of the source animal(s) (section 3).

2.5. Written Informed Consent and Recipient Education

In the process of obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) (e.g., 45 CFR part 46; 21 CFR part 50), and should adhere to good clinical practices and to the ethical principles derived from the Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The informed consent discussion, the written informed consent form, and the written information provided to subjects should address the following points relating to the risk of xenotransplantation:

2.5.1. The potential for infection from zoonotic agents known to be associated with the donor species.

2.5.2. The potential for transmission of unknown xenogeneic infectious agents to the recipient. The patient should be informed of the uncertainty regarding these risks, the possibility that infections with these agents may not be recognized for some time, and that the nature of clinical diseases that these agents may cause are unknown.

2.5.3. The potential risk for transmission of xenogeneic infectious agents to the recipient's family or close contacts, especially sexual contacts. Close contacts are defined as household members and others with whom the recipient participates in activities that could result in exchanges of body fluids. The recipient should be informed that transmission of these agents may be minimized by the use of barriers during sexual intercourse and that infants, pregnant women, elderly, and chronically ill or immunosuppressed persons may be at increased risk for infection from zoonotic or opportunistic agents (section 4.2).

2.5.4. Any need for isolation procedures during hospitalization (including the estimated duration of such confinement), and any specialized precautions (e.g., dietary, travel) following hospital discharge.

2.5.5. The need to comply with long-term or potentially life-long surveillance necessitating routine physical evaluations with archiving of tissue and/or serum specimens. The schedule for clinical and laboratory monitoring should be provided to the extent possible. The patient should be informed that any serious or unexplained illness in themselves or their contacts should be reported to their physician immediately.

2.5.6. The need for the subject to inform the investigator or his/her designee of any change in address or telephone number in order to maintain accurate data for long-term health surveillance.

2.5.7. Discussion with the patient regarding performance of a complete autopsy. Joint discussion with the recipient and his/her family concerning the need to conduct an autopsy is also encouraged in order to communicate the recipient's intent.

2.5.8. Access by the appropriate public health agencies to all medical records. To the extent permitted by applicable laws and/or regulations, the confidentiality of medical records will be maintained.

2.5.9. Consent forms should state clearly that xenograft recipients should never, subsequent to receiving the transplant, donate Whole Blood, blood components, Source Plasma, Source Leukocytes, tissues, breast milk, ova, sperm, or any other body parts for use in humans.

3. Animal Sources For Xenotransplants

Recognized zoonotic infectious agents and other organisms present in animals, such as normal flora or commensals, may cause disease in humans when introduced by transplantation of cells, tissues, or organs, especially in immunocompromised patients. The ability to screen extensively the cells, tissues, or organs intended for clinical use may be limited by the need to ensure graft viability. The risk of transmitting infectious agents can be minimized by procurement of source animals from herds or colonies that are screened and qualified as pathogen free for specific agents appropriate for the clinical application, and are maintained in an environment that minimizes exposure to vectors of infectious agents.

3.1. Animal Procurement Sources

3.1.1. Cells, tissues, and organs intended for use in xenotransplantation should be procured only from animals with documented lineages and that have been bred and reared in captivity.

3.1.2. Animals should be obtained from closed herds or colonies that are serologically well-characterized and as free as possible of infectious agents of concern for the animal species and the patient.

3.1.3. The use of animals from controlled environments such as closed corrals (captive free-ranging animals) should be used only when they are the only suitable source for a given xenotransplant procedure. Such animals require more intensive screening because of the higher likelihood that they harbor adventitious infectious agents from uncontrolled contact with arthropods and/or other animals.

3.1.4. Wild-caught animals should not be used as sources for cells, tissues, or organs intended for transplantation.

3.1.5. Imported animals or the first generation of offspring of imported animals should not be used as a source of cells, tissues, or organs unless the animals belong to a species or strain not available for use in the United States. In this case, their use should be considered only if the source characteristics for the imported animals can be documented, validated, and audited.

3.1.6. Source animals from species in which prion-mediated diseases (e.g., transmissible spongiform encephalopathies) have been reported should be obtained from closed herds with documented absence of dementing illnesses and controlled food sources (section 3.2.1.3). Bovine transplant tissue should not be obtained from countries designated by the United States Department of Agriculture (USDA) as those where bovine spongiform encephalopathy (BSE) exists (59 FR 44591, August 29, 1994, and 60 FR 44036, August 24, 1995).

3.1.7. Animals or live animal cells, tissues, or organs obtained through abattoirs should not be used as a source of xenografts. These animals are obtained from geographically divergent farms or markets and are more likely to carry infectious agents due to increased exposure to other animals, and increased activation and shedding of infectious agents during the stress of slaughter. In addition, health histories

of slaughterhouse animals are usually not available.

3.2. Biomedical Research Animal Facilities

For the purposes of xenotransplantation, animals should be housed in facilities built and operated in accordance with standards outlined in this section. As a minimum, these facilities should meet the recommendations of the Guide for the Care and Use of Laboratory Animals (the criteria for accreditation by the American Association for the Accreditation of Laboratory Animal Care (AAALAC)) and be subject to inspection by appropriate members of the transplant teams and public health agencies. Animal facilities should have a routine well-documented herd health and surveillance system. Animal facilities should have on staff veterinarians with expertise in the infectious diseases prevalent in the animal species and should maintain active collaboration with accredited microbiology laboratories.

3.2.1. The biomedical animal facility standard operating procedures should be thoroughly described regarding the following: (1) Criteria for animal admission; (2) description of the disease monitoring program; (3) criteria for the isolation or elimination of diseased animals; (4) criteria for the health screening and surveillance of humans entering the facility; (5) facility cleaning arrangements; (6) the source and delivery of feed, water, and supplies; (7) measures to exclude arthropods and other animals; (8) animal transportation; and (9) dead animal disposition. Entry and exit of animals, animal care staff, and other humans should be controlled to minimize environmental exposures/inadvertent exposure to transmissible infectious agents.

3.2.1.1. Animal movement through the secured facility should be described in the standard operating procedures of the facility. All animals introduced into the source colony other than by birth should go through a well-defined quarantine and testing period (section 3.5). With regard to the reproduction and raising of suitable animals, the use of methods such as artificial insemination (AI), embryo transfer, medical early weaning (MEW), cloning, or hysterotomy/hysterectomy and fostering may minimize further colonization with infectious agents.

3.2.1.2. During final screening and qualification of individual source animals and xenograft procurement, the potential for transmission of an infectious agent is minimized by utilizing a step-wise ''batch'' or ''all-in/all-out'' method of source animal movement through the facility rather than continuous replacement movement. With the ''all-in/all-out'' or ''batch'' method, one or more individual source animals are selected from the closed herd or colony and quarantined while undergoing final screening qualification and graft procurement. After the entire batch of source animals is removed, the quarantine and graft processing areas of the animal facility are then washed and disinfected prior to the introduction of the next batch of source animals.

3.2.1.3. The feed components, including any medicinals or other additives, should be documented for a minimum of one generation prior to the source animal. The absence of recycled or rendered animal materials in feed should be specifically documented. The absence of such materials is important for the prevention of prion-associated diseases and slow viral infections, as well as for the prevention of transmission of other infectious agents. Potentially extended periods of clinical latency, severity of consequent disease, and the difficulty in current detection methods highlight the importance of eliminating risk factors associated with prion transmission.

3.2.1.4. Facilities supplying research animals for use in xenotransplant protocols should maintain a source animal record system that documents every animal, organ, tissue, or type of cells supplied for transplantation, and the transplant centers where these were sent. Facilities should maintain records of the following: the lifelong health history of the source animals (section 3.5), the herd health surveillance (sections 3.3, 3.4), and the standard operating procedures of the animal procurement facility (section 3.2). An animal numbering or other identifier system should be employed to allow easy, accurate, and rapid linkage between the information contained in these different record systems.

3.2.1.5. In the event that the biomedical animal facility ceases to operate, all animal health records and specimens should be transferred to the respective clinical transplant centers or the centers should be notified of the new archive site.

3.3. Preclinical Screening for Known Infectious Agents

The following points discuss measures for appropriate screening of known infectious agents in the herd, individual source animal, and the xenograft (sections 3.4, 3.5, 3.6).

3.3.1. Preclinical studies should be performed in conjunction with the development of specific clinical applications for the use of xenografts. These preclinical studies should be species specific in the identification of microbial agents in xenografts. These studies should characterize the potential of identified agents for human pathogenicity. Characterization of the human pathogenicity of xenotropic endogenous retroviruses and persistent viral infections present in source animal cells, tissues, and organs is particularly important.

3.3.1.1. These preclinical studies should identify appropriate assays for the screening program to qualify xenografts for clinical use.

3.3.2. Programs for screening and detection of known infectious agents in the herd or colony, the individual source animal, and the xenograft should be tailored for the source animal species and clinical application and be updated periodically to reflect advances in the knowledge of infectious diseases. The xenotransplant team should be responsible for the adequacy of the screening program.

3.3.3. All assays used for the screening and detection of infectious agents (both commensals and pathogens) in the herd or colony, in the individual source animal, and in the final analysis of the xenograft should have well documented specificity and sensitivity as well as validity in the setting in which they are employed. Assays under development may complement the screening process.

3.3.4. Samples from xenografts should be tested preclinically with cocultivation assays that include a panel of appropriate indicator cells, including human peripheral blood mononuclear cells (PBMC), to facilitate amplification and detection of xenotropic endogenous retroviruses and other xenogeneic viruses capable of producing infection in humans. The selection of indicator cells on the cocultivation panel should be determined by the xenograft and its clinical applications. For instance, xenotransplantation involving the human central nervous system (CNS) may warrant cocultivation of samples from the xenograft with a human neuronal cell line in the attempt to detect neurotropic viruses. Serial blind passages and observation for cytopathic effect, focus formation, reverse transcriptase assay, and electron microscopy may be appropriate. When cultures suggest the presence of viral agents, immunologic or genetic techniques (enzyme immunoassays for detection of serologic cross-reactivity, immunofluorescence or other immunoassays, Southern blot analysis, polymerase chain reaction (PCR)

techniques, PCR-based reverse transcriptase assay etc.) or cross-species in vivo culturing techniques may be useful. Detection of latent viruses may be facilitated by their activation using chemical and irradiation methods. For detection of possible bacteria, universal PCR probes are available and should be considered for screening of xenografts.

3.4. Herd/Colony Health Maintenance and Surveillance

The principal elements recommended to qualify a herd or colony as a source of animals for use in xenotransplantation include: (1) Closed herd or colony, and (2) adequate surveillance programs for infectious agents. Documentation of the herd or colony health maintenance and surveillance program relevant to the specific application should be available in the standard operating procedure of the animal facility. These procedures should be available to the review committees. Permanent medical records for the herd or colony and the specific individual source animals should be maintained indefinitely at the animal facility.

3.4.1. Herd or colony health measures that constitute standard veterinary care for the species (e.g., anti-parasitic measures) should be implemented and recorded at the animal facility. For example, aseptic techniques and sterile equipment should be used in all parenteral interventions including vaccinations, phlebotomy, and biopsies. All incidents that may affect herd or colony health should be recorded (e.g., breaks in the environmental barriers of the secured facility, disease outbreaks, or sudden animal deaths). Vaccination and screening schedules should be described in detail. The use of live vaccines is discouraged but may be justified when dead or acellular vaccines are not available. Their use should be documented and taken into account in the risk assessment.

3.4.2. In addition to standard medical care, the herd/colony should be monitored for the introduction of infectious agents which may not be apparent clinically. The standard operating procedures should describe this monitoring program, including the types and the schedules of physical examinations and laboratory tests used in the detection of infectious agents.

3.4.3. Routine testing of closed herds or colonies in the United States should concentrate on zoonoses known to exist in captive animals of the relevant species in North America. Because many important pathogens are not endemic to the United States or have been found only in wild-caught animals, testing of breeding stock and maintenance of a closed herd or colony reduces the need for extensive testing of individual source animals. Herd or colony geographic locations are relevant to consideration of presence and likelihood of pathogens in a given herd or colony. Veterinarians familiar with the prevalence of different infectious agents in the geographic area of source animal origin and the location where the source animals are to be maintained should be consulted.

3.4.3.1. As part of the surveillance program, routine serum samples should be obtained from randomly selected animals representative of the herd or colony population. These samples should be tested for infectious agents relevant to the species and epidemiologic exposures. Additional directed serologic analysis or active culturing of individual animals should be performed in response to clinical indications. Infection in one animal in the herd justifies a larger clinical and epidemiologic evaluation of the rest of the herd or colony. In addition, serum samples should be stored indefinitely at the animal research facility for investigation of unexpected disease either in the herd or colony, individual source animals, or in the xenograft recipient or contacts.

3.4.3.2. Any animal deaths where the cause is unknown or ambiguous, including all fetal stillbirths or abortions, should lead to full necropsy and evaluation for infectious etiologies with documentation.

3.4.3.3. Standard operating procedures that maintain a subset of sentinel animals for the duration of their natural life are encouraged. Life-long monitoring of these animals will increase the probability of detection of subclinical, latent or late-onset diseases such as prion-mediated disease.

3.5. Individual Source Animal Screening and Qualification

The qualification of indivudal source animals should include breed and lineage, and documentation of general health, including vaccination history with attention to use of any live attenuated vaccines. The presence of pathogens resulting in acute infections should be controlled for by clinical examination and treatment of individual source animals, by use of appropriate individual quarantine periods that extend beyond the incubation period of pathogens of concern, and by herd surveillance indicating the presence or absence of infection in the herd from which the individual source animal is selected. During quarantine, individual source animals should be screened for infectious agents relevant to the particular clinical application.

3.5.1. Individual source animals should be quarantined for at least 3 weeks prior to xenograft procurement. During this time, acute illnesses due to infectious agents to which the animal may have been exposed shortly before removal from the herd or colony would be expected to become clinically apparent. It may be appropriate to modify this quarantine period depending upon the characterization and surveillance of the source animal herd or colony and the clinical urgency. When the quarantine period is shortened, justification should be documented in the protocol and the potentially increased infectious risk incurred should be addressed in the informed consent document.

3.5.1.1. During the quarantine period, candidate source animals should be screened for the presence of infectious agents (bacteria, parasites, and viruses) by appropriate serologies and cultures, complete blood count and peripheral blood smear, and fecal exam for parasites. The screening program should be guided by the surveillance and health history of the herd or colony. Evaluation for viral agents which may not be recognized zoonotic agents but which have been documented to infect either human or non-human primate cells in vivo or in vitro should be considered. Particular attention should be given to viruses with demonstrated capacity for recombination, complementation, or pseudotyping. These tests should be performed as closely as possible to the date of transplantation while ensuring availability of results prior to clinical use.

3.5.1.2. Screening of a candidate source animal should be repeated prior to xenograft procurement if a period greater than 3 months has elapsed since the initial screening and qualification was performed (e.g., if the planned xenograft was not procured or a second xenograft is obtained) or if the animal has been in contact with other nonquarantined animals between the quarantine period and the time of cells, tissue or organ procurement.

3.5.1.3. Transportation of source animals may compromise the protection ensured by the closed colony. Careful attention to conditions of transport can minimize but not eliminate disease exposures during shipping. A more extensive period of quarantine and screening comparable to that used for entry of new animals into a closed herd or colony should be instituted upon arrival. Xenografts should be procured, when feasible, at the animal facility and

transported as the cells, tissues, or organ to be transplanted.

3.5.2. All procured cells, tissues, and organs intended for clinical use should be as free of infectious agents as possible. When feasible, the use of source animals in whom infectious agents, including latent viruses, have been identified should be avoided. The presence of an agent in certain anatomic sites, for example the alimentary tract, may not preclude use of the source animal if the agent is documented to be absent in the xenograft.

3.5.3. If feasible and when it is unlikely to compromise the xenograft, a biopsy should be studied for infectious agents by appropriate screening assays (section 3.3) and appropriate histopathology prior to transplantation, and then archived (section 3.7). The results from all studies should be reviewed by the principal investigator prior to clinical use of the xenograft.

3.5.4. The sources, relevant husbandry, and health history (including use as experimental subjects) of herds and/or individual source animals should be available to the reviewing committees. All relevant health records for the life of the animal, including both the herd and the individual source animal records and a full history of vaccinations, should be available and reviewed prior to candidate animal selection and procurement of cells, tissues, and organs. These records should be maintained indefinitely for retrospective review. A copy of the individual source animal record should accompany the xenograft and be archived as part of the permanent medical record of the xenograft recipient.

3.5.5. The biomedical animal facility should notify the clinical center in the event that an infectious agent is identified in the source animal or herd subsequent to xenograft harvest (e.g., identification of delayed onset prion-mediated disease in a sentinel animal).

3.6. Procurement and Screening of Xenografts

3.6.1. Procurement and processing of cells, tissues, and organs should be performed using documented aseptic conditions designed to minimize contamination. These procedures should be conducted in designated facilities which are subject to inspection.

3.6.2. Procedures that may inactivate or remove pathogens without compromising the integrity and function of the xenograft should be employed.

3.6.3. Cells, tissues, or organs intended for transplantation that are maintained in culture prior to transplant should be periodically screened for maintenance of sterility, including screening for viruses and mycoplasma (section 3.3.4). The FDA publications entitled ''Points to Consider in Somatic Cell and Gene Therapy (1991),'' ''Points To Consider in the Characterization of Cell Lines Used to Produce Biologicals (1993),'' and ''Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals (1995)'' should be consulted for guidance.

3.6.4. To ensure reproducible quality control of the procurement and screening process, all events involved in procurement of the xenograft up to the point of transplanting the tissue into the patient should be rehearsed and documented.

3.6.5. When the animal is euthanatized during procurement of the cells, tissue, or organ, a full necropsy should be conducted including gross, histopathological, and microbiological evaluation. When xenografts are procured without euthanatizing the source animal, the animal's health should be monitored for life. When these animals die or are euthanatized, a full necropsy should follow, regardless of the time elapsed between graft procurement and death. The results of the necropsy, documented in the animal's permanent medical record, should be archived indefinitely. In the event that the necropsy findings suggest infections pertinent to the health of the xenograft recipient(s) (e.g., evidence of prion-associated disease) the finding should be communicated to all transplant centers that receive cells, tissues, or organs from this source animal (section 3.5.5.).

3.7. Archives or Source Animal Medical Records and Specimens

Systematically archived source animal biologic samples and recordkeeping that allows rapid and accurate linking of xenograft recipients to the individual source animal records and archived biologic specimens are essential for public health investigation and containment of emergent xenogeneic infections.

3.7.1. Responsibility for the care of, and access to, tissue archiving and recordkeeping should be clearly designated in the research and clinical protocol.

3.7.2. Animal source herd or colony health records, individual source animal health records, and records of the screening analysis of the xenograft should be maintained indefinitely. A summary of the individual source animal health record and a record of the xenograft screening qualification should be filed at the clinical transplant site as part of the xenotransplant recipient medical record.

3.7.3. For the purposes of retrospective public health investigations, source animal biologic specimens should be banked at the time of graft procurement and designated for public health. All specimens should remain in archival storage indefinitely to permit retrospective analysis if a public health need arises (section 4.1.1.4.). Archived source animal biologic specimens should be readily accessible and linkable to both source animal and recipient(s) health records.

3.7.4. Ideally, at least five 0.5cc aliquots of each source animal serum and plasma should be banked. At least three aliquots of viable (1×10^7) leukocytes should be cryopreserved. Optimally, DNA and RNA extracted from leukocytes should also be aliquoted and banked. Additionally, paraffin-embedded, formalin fixed, and cryopreserved tissue samples representative of major organ systems (e.g., spleen, liver, bone marrow, central nervous system) should be collected from source animals euthanatized concomitant with procurement of the xenograft.

4. Clinical Issues

4.1. Xenotransplant Recipient

4.1.1. Surveillance of the xenotransplant recipient. Post-transplantation clinical and laboratory surveillance of xenograft recipients is critical to monitor for the introduction and propagation of xenogeneic infectious agents in the general population. Performance and documentation of this surveillance should be the responsibility of the clinical center and should continue throughout the life of the recipient. Appropriate surveillance methods include the following:

4.1.1.1. Adverse clinical events potentially associated with xenogeneic infections should be evaluated during periodic clinic visits following the transplant procedure.

4.1.1.2. Biological specimens should be collected and archived to allow retrospective investigation of possible xenogeneic infections. These biological specimens should be designated for public health investigative purposes. Specimens to be collected should be appropriate to the specific transplant situation. Serum, plasma, and peripheral blood mononuclear cells (PBMC's) should be collected. Preferably, at least three to five 0.5cc aliquots of citrated or EDTA-anticoagulated plasma should be banked

at the predetermined time points outlined below. At least 2 aliquots of viable leukocytes (1×10^7) should be cryopreserved. Additionally, DNA and RNA extracted from leukocytes (1×10^7) and/or sera could be aliquoted and banked. Specimens of any xenograft that is removed (e.g., post-rejection or at time of death) should be banked.

The following schedule for archiving biological specimens is recommended: (1) Two sets of samples should be archived 1 month apart before the xenotransplant procedure. If this is not feasible then two sets should be archived as temporally separated as possible, (2) a set should be archived in the immediate posttransplant period and at approximately 1 month and 6 months post transplantation, (3) collection should then be obtained annually for the first 2 years after transplant, (4) After that, specimens should be archived every 5 years for the remainder of the recipient's life. More frequent archiving may be indicated by the specific protocol or the recipient's medical course.

4.1.1.3. In the event of death of the recipient, snap-frozen samples store at −70° C, paraffin embedded tissue, and tissue suitable for electron microscopy should be collected at autopsy from the xenograft and all major organs relevant to either the transplant or the clinical syndrome resulting in death. These specimens should be archived indefinitely for potential public health use.

4.1.1.4. The clinical center should be responsible for maintaining an ongoing and accurate archive of biologic specimens. In the absence of a central facility (section 5.2) the designated public health biologic specimens should be archived with appropriate safeguards to ensure long-term storage (e.g., a monitored storage freezer alarm system and specimen archiving in split portions in separate freezers) and an efficient system for the prompt retrieval and linkage of data to medical records of recipients and source animals.

4.1.1.5. In addition to archiving of biologic specimens, active laboratory surveillance program of the xenograft recipient should be instituted when xenogeneic agents are known or suspected to be present in the xenograft. The intent of active screening in this setting is detection of sentinel human infections prior to dissemination in the general population. Serum, PBMC's, or tissue should be assayed at periodic intervals post transplantation for xenogeneic agents known to be present in the transplanted tissue. Active surveillance should include more frequent screening in the immediate posttransplant period (e.g., at 2, 4, and 6 weeks after transplantation) with subsequently decreasing frequency in the absence of clinical indication. Assays intended for the generic detection of unknown agents may also be appropriate. Assays should be used to detect classes of viruses known to establish persistent latent infections in the absence of clinical symptoms (e.g., herpesviruses and retroviruses) (section 3.3.1.1.). When the xenogeneic viruses of concern have similar human counterparts, e.g., simian CMV, assays to distinguish between the two should be employed. Depending upon the degree of immunosuppression in the recipient, serological assays may be or may not be useful. Methods for analysis include cocultivation of cells coupled with appropriate detection assays. The sensitivity, specificity, and validity of the testing methods should be predetermined and documented under conditions simulating those employed in the xenotransplant procedure.

4.1.1.6. In response to a potential xenogeneic infection related to a clinical episode, posttransplantation testing of archived biologic specimens should be conducted in association with an epidemiologic investigation to assess potential public health significance of the infection. This investigation should proceed under the direction of appropriate health authorities following prompt notification of the State health department, CDC, and FDA.

4.2. Contacts of Recipient

The clinical protocol should outline a procedure to inform the recipient of the responsibility to educate his/her close contacts regarding the possibility of the emergence of xenogeneic infections from the source animal species and to offer the recipient assistance with this education process, if desired. Education of close contacts should address the uncertainty regarding the risks of xenogeneic infections, information about behaviors known to transmit infectious agents from human to human (i.e., unprotected sex, intravenous drug use with shared needles and other activities that involve potential exchange of blood or other body fluids) and methods to minimize the risk of transmission. Recipients should educate their close contacts about the need to inform their physician and the research coordinator at the institution where the xenotransplantation was performed of any significant unexplained illnesses in themselves or their close contacts.

4.3. Hospital Infection Control

4.3.1. Infection Control Practices

4.3.1.1. Standard precautions should be used for the care of all patients, including appropriate handwashing, use of barrier precautions, and care in the use and disposal of needles and other sharp instruments. Strict adherence to these recommended procedures will reduce the risk of transmission of xenogeneic infections and other blood-borne and nosocomial pathogens.

4.3.1.2. Additional infection control or isolation precautions (e.g., airborne, droplet, contact) should be employed as indicated in the judgment of the hospital epidemiologist and the xenotransplant team infectious disease specialist. For example, appropriate isolation precautions for each hospitalized transplant recipient will depend upon the xenotransplant, the extent of immunosuppression, and the clinical condition of the recipient. The appropriateness of infection control measures should be considered at the time of transplant and reevaluated during each readmission. Isolation precautions should be continued until a suspected xenogeneic infection has been proven and resolved or has been effectively ruled out in the recipient.

4.3.1.3. Xenotransplant teams should adhere to recommended procedures for handling and disinfection/sterilization of medical instruments and disposal of infectious waste.

4.3.2. Acute Infectious Episodes. Most acute viral infectious episodes among the general population are never etiologically identified. Xenograft recipients remain at risk for these infections and other infections common among immunosuppressed allograft recipients. When the source of a significant illness in a recipient remains unidentified despite standard diagnostic procedures, more testing of body fluid and tissue samples may be appropriate. The infectious disease specialist, in consultation with the hospital epidemiologist, the veterinarian, the clinical microbiologist and other members of the xenotransplant team should assess each clinical episode and make a considered judgment regarding the need and type of diagnostic testing and appropriate infection control precautions. Experts on infectious diseases and public health may also need to be consulted.

4.3.2.1. Immunosuppressed transplant patients may be unable to mount a sufficient immunological response for serological assays to detect infections reliably. In this setting, appropriate validated culture systems, genomic detection methodologies and other

techniques may detect diseases for which serologic testing is inadequate. Consequently, clinical centers where xenotransplantation is performed should have the capability to culture and to identify viral agents using in vitro and in vivo methodologies. Specimens should be handled to ensure their viability and to maximize the probability of isolation and identification of fastidious agents. Algorithms for evaluation of unknown xenogeneic pathogens should be developed in consultation with appropriate experts, including persons with expertise in both medical and veterinary infectious diseases, laboratory identification of unknown infectious agents and the management of biosafety issues associated with such investigations.

4.3.2.2. Archiving of acute and convalescent sera obtained in association with acute unexplained illnesses should be performed when appropriate as judged by the infectious disease physician and/or the hospital epidemiologist. This would permit retrospective study and perhaps an etiologic diagnosis of the clinical episode.

4.3.3. Health Care Workers. A comprehensive occupational health services program should be designed to educate workers regarding the risks associated with xenotransplantation and to monitor for possible infections in workers. Health care workers, including laboratory personnel, who handle the animal tissues/organs prior to transplantation will have a definable risk of infection not exceeding that of animal care, veterinary, or abattoir workers routinely exposed to the source animal species provided equivalent biosafety standards are employed. However, the risk to health care workers who provide direct/indirect post-transplantation care for xenograft recipients is undefined. Decisions regarding work restrictions or assignments for immunocompromised workers should be determined by each institution. The occupational health services program should include the following:

4.3.3.1. Education of Health Care Workers. All centers where xenotransplantation procedures are performed should develop appropriate educational materials for their staff tailored to each procedure. These materials should describe the xenotransplant procedure(s), and the known and potential risks of xenogeneic infections posed by the procedure(s). Those research or health care activities that are considered to be associated with the greatest risk of infection should be emphasized in order to minimize exposure and transmission of both zoonotic and nosocomial agents between the recipient and the health care workers. The use of Standard Precautions should be reviewed. Education programs should detail the circumstances for use of personal protective equipment (e.g., gloves, gowns, masks, etc.) and the importance of handwashing before and after all patient contacts, even if gloves are worn. The potential for transmission of these agents to the general public should be discussed.

4.3.3.2. Worker Surveillance. Protocols should be developed for the collection and archiving of baseline sera (i.e., prior to exposure to xenografts or recipients) from health care workers either on the xenotransplant team or caring for xenograft recipients and any laboratory personnel who may handle the animal cells, tissues, and organs or future biologic specimens from transplant recipients. Archived sera serve as a baseline specimen for comparing sera collected following nosocomial exposures. In addition, these protocols should describe methods of recording, storing, and retrieving information related to health care workers and specific nosocomial exposures. The activities of the Occupational Health Service should be coordinated with the Infection Control Program to ensure appropriate surveillance of infections in personnel.

4.3.3.3. Postexposure Evaluation and Management. Written protocols should be in place for the evaluation of health care workers who experience an exposure where there is a risk of transmission of an infectious agent, e.g., an accidental needlestick. Health care workers, including laboratory personnel, should be instructed to report exposures immediately to the Occupational Health Service. The postexposure protocol should describe the information to be recorded including the date and nature of exposure, the xenotransplantation procedure, recipient information, actions taken as a result of such exposures (e.g., counseling, postexposure management and followup) and the outcome of the event. This information should be archived in a Health Exposure Log (section 4.4) and maintained indefinitely at the xenotransplantation center despite any change in employment of the health care worker or discontinuation of xenotransplantation procedures at that center. Health care and laboratory workers should be counseled to report and seek medical evaluation for unexplained clinical illnesses occurring after the exposure.

4.4. Health Care Records

Each clinical xenotransplantation center should maintain indefinitely the three cross-referenced record systems: (1) An Institutional Xenotransplantation Record which documents for all xenotransplant procedures: The principal investigator, the individual source animal and its procurement facility, the date and type of procedure, the xenograft tissue recipient and a summary of the recipient's clinical course, close contacts, and the health care workers associated with each procedure; (2) a Xenotransplantation Nosocomial Health Exposure Log which documents the dates, involved persons, and nature of all nosocomial exposures which are associated with a xenotranplantation protocol and which potentially pose risk of transmission of xenogeneic infections; (3) individual xenotransplant recipient health records which document comprehensively each patient's clinical course, the results of post-transplant surveillance studies (section 4.1), and contain a summary of both the health status report and the results of the screening assays performed on source animal(s) from which the xenograft was obtained.

These records should be current and accurately cross-referenced. This systematic data maintenance will facilitate epidemiologic investigation of adverse events. In the future, these data should be linked to any national registry (section 5.1) to facilitate recognition of rates of occurrence and clustering of adverse health events, including events that may represent the outcomes of xenogeneic infections and mortality patterns, and linkage of those events to specific exposures on a national level.

5. Public Health Needs

5.1. National Registry

The public health interest would best be served by the establishment of a national registry. A national registry would enable rapid identification of epidemiologically significant common features among xenograft recipients and provide a data base for the assessment of long-term safety. Such a data base would make possible the rapid recognition of rates of occurrence and clustering of health events that may represent outcomes of xenogeneic infections; allow the accurate linkage of these events to exposures on a national level; facilitate notification of individuals and clinical centers regarding epidemiologically significant adverse events associated with

xenotransplantation; and enable biological and clinical research assessments. Information derived from the registry should be reasonably available to the public with appropriate confidentiality protection for any patient identifying information and/or proprietary information.

5.2 Serum and Tissue Archives

Samples of sera, plasma, leukocytes, and tissue of the source animal and recipient should be archived for public health investigation purposes as discussed in sections 3.7 and 4.1. Source animal and xenograft recipient specimens should be kept at individual centers under storage conditions outlined in section 4.1.1.4. Information about the location and nature of archived specimens associated with each transplant should be documented in the health care records and delineated in sections 3.7 and 4.4, and ultimately in any national registry that is established.

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The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. References 1 through 5 may also be obtained from FDA/CBER/ Office of Communication, Training and Manufacturers Assistance via FAX by calling 1–800–835–4709 or via mail by calling 301–827–1800. References 21 through 24 may also be obtained from The National Technical Information Service (NTIS), 5285 Port Royal Rd., Springfield, VA 22161, 703–487–4650.

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4. The National Organ Transplant Act (42 U.S.C. 273 *et seq.*).
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F. Clinical Issues

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