PREAMBLE

PHS Guideline on Infectious Disease Issues in Xenotransplantation

Background

Several developments have fueled the renewed interest in xenotransplantation– the use of live animal cells, tissues and organs in the treatment or mitigation of human disease. The world-wide, critical shortage of human organs available for transplantation and advances in genetic engineering and in the immunology and biology of organ/tissue rejection have renewed scientists' interest in investigating xenotransplantation as a potentially promising means to treat a wide range of human disorders. This situation is highlighted by the fact that in the United States alone, 13 patients die each day waiting to receive a life-saving transplant to replace a diseased vital organ.

While animal organs are proposed as an investigational alternative to human organ transplantation, xenotransplantation is also being used in the effort to treat diseases for which human organ allotransplants are not traditional therapies (e.g., epilepsy, chronic intractable pain syndromes, insulin dependent diabetes mellitus and degenerative neurologic diseases such as Parkinson's disease and Huntington's disease). At present, the majority of clinical xenotransplantation procedures utilize avascular cells or tissues rather than solid organs in large part due to the immunologic barriers that the human host presents to vascularized xenotransplantation products. However, with recent scientific advances, xenotransplantation is viewed by many researchers as having the potential for treating not only end-organ failure but also chronic debilitating diseases that affect major segments of the world population.

Although the potential benefits may be considerable, the use of xenotransplantation also presents a number of significant challenges. These include (1) the potential risk of transmission of infectious agents from source animals to patients, their close contacts, and the general public;
(2) the complexities of informed consent; and (3) animal welfare issues.

On September 23, 1996, the Department of Health and Human Services (DHHS) published for public comment the *Draft PHS Guideline on Infectious Disease Issues in Xenotransplantation* to address the infectious disease concerns raised by xenotransplantation (61 Federal Register 49919). The Draft Guideline was jointly developed by five components within DHHS–the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), National Institutes of Health (NIH), all parts of the U.S. Public Health Service (PHS), plus the DHHS Office of the Assistant Secretary for Planning and Evaluation. This Draft Guideline discusses general principles for the prevention and control of infectious diseases that may be associated with xenotransplantation. Intended to minimize potential risks to public health, these general principles provide guidance on the development, design, and implementation of clinical protocols to

sponsors of xenotransplantation clinical trials and local review bodies evaluating proposed xenotransplantation clinical protocols. The Draft Guideline emphasizes the need for appropriate clinical and scientific expertise on the xenotransplantation research team, adequate protocol review, thorough health surveillance plans, and comprehensive informed consent and education processes.

In response to the Draft Guideline, the DHHS received over 140 written comments reflecting a broad spectrum of public opinion (Federal Register docket No. 96M-0311). Comments were received from a variety of stakeholders, including representatives of academia; industry; patient, consumer, and animal welfare advocacy organizations; professional, scientific and medical societies; ethicists; researchers; other government agencies and private citizens.

In revising the Draft Guideline, careful consideration was given to recent scientific findings, each of the written comments, as well as to public comments received at several national, international, and DHHS-sponsored workshops. These meetings constituted critically important public forums for discussing the scientific, public health, and social issues attendant to xenotransplantation.

The DHHS sponsored two public workshops on xenotransplantation during 1997 and 1998. The first meeting, held in July 1997, focused on virology and documented evidence of cross species infections. Titled "Cross-Species Infectivity and Pathogenesis," the meeting addressed current knowledge about the mechanisms and consequences of infectious agent transmission across species barriers. Discussions also focused on the possibility that an infectious agent might cross from an animal donor organ or tissue to human xenotransplantation product recipients. The conference also highlighted gaps in knowledge about the emergence of new infections in humans, especially as a result of xenotransplantation. The basic consensus of the meeting was that while there were examples of animal infectious agents crossing species barriers to infect, and even cause diseases in humans, the actual likelihood of this in xenotransplantation product recipients cannot be ascertained at this time. Small adequate and well-controlled clinical trials designed to test the safety and efficacy of xenotransplantation were considered to be appropriate. One anticipated outcome of such trials would be to both minimize and better understand the risks of transmission of infectious agents. (The meeting summary can be accessed at: http://www.niaid.nih.gov/dait/cross-species/default.htm)

In January 1998, a second DHHS workshop titled "Developing U.S. Public Health Service Policy in Xenotransplantation," focused on the current and evolving U.S. public health policy in xenotransplantation. (The meeting transcripts can be accessed at http://www.fda.gov/ohrms/dockets/dockets /96m0311 /96m0311.htm) Among other issues, the regulatory framework, a national xenotransplantation database, and a national advisory committee were discussed.

During this workshop, several themes were raised repeatedly and echoed many of the written public comments on the Draft Guideline. First, there was a broad consensus that the Draft Guideline was

important and should be implemented, albeit with some modifications. For example, it was expressed that there could be more public awareness and participation in the development of public health policies in the field of xenotransplantation. Second, there was strong support for the DHHS proposal to establish a national xenotransplantation advisory committee, not only to facilitate analysis and discussion of the scientific, medical, ethical, legal, and social issues raised by xenotransplantation, but also to review and make recommendations about proposed clinical trial protocols. There was broad support for proceeding cautiously with xenotransplantation trials; however, some participants held that a national moratorium on clinical trials in xenotransplantation might be advantageous until the national xenotransplantation advisory committee is established and operational. While there is no definitive scientific evidence that xenotransplantation would promote cross-species infectious agent transmission *leading to disease*, there are data providing a reasonable basis for caution [see revised guideline, section 6., references D.1.a; e.; f.; i.; l; o.; q.; r.& s.]. Some members of the scientific and medical community and concerned citizens expressed the opinion that there is a perceived greater risk from the use of xenotransplantation products procured from nonhuman primates (as opposed to other species) because of potential public health risks and animal welfare concerns.

The January 1998 workshop also included presentations by representatives of the World Health Organization (WHO), the Organization for Economic Cooperation and Development (OECD), and several nations engaged in developing policies on xenotransplantation. These presentations placed the U.S. policy in global context and enhanced international dialogue on important public health safeguards. Because of the potential for the secondary transmission of infectious agents, the public health risks posed by xenotransplantation transcend national boundaries. International communication and cooperation in the development of public health policies are critical elements in successfully addressing the global safety and ethical challenges inherent in xenotransplantation. To this end, several countries, including Canada, France, Germany, the Netherlands, Spain, Sweden, the United Kingdom, and the United States and several international organizations such as the WHO, OECD, and the Council of Europe are actively engaged in international workshops and consultations on xenotransplantation. [see revised guideline, section 6.C.7. for a partial bibliography of guidance documents and websites from national and international bodies].

Major Revisions and Clarifications to the Guideline

Major revisions and clarifications to the Draft Guideline are briefly summarized and discussed below. These revisions were prompted by public comments submitted to the Draft Guideline docket, concerns expressed at public workshops, evolving science, and developing international policies. PHS intends to address related issues that go beyond the scope of this Guideline in future guidance documents. In the future the Guideline may be amended as needed to appropriately reflect the accrual of new knowledge about cross-species infectivity and pathogenesis, new insights into the potential risks associated with xenotransplantation, policies currently under development (e.g., the Secretary's Advisory Committee on Xenotransplantation and the National Xenotransplantation Database), and other evolving public

health policies in this arena.

Definition of Xenotransplantation and Xenotransplantation Product. The definition of "xenotransplantation" has been revised from that used in the Draft Guideline. For the purposes of this document and US PHS policy xenotransplantation is now defined to include 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. Furthermore, xenotransplantation products have been defined to include live cells, tissues or organs used in xenotransplantation. The term xenograft, used in previous PHS documents, will no longer be used to refer to all xenotransplantation products.

Clinical Protocol Review and Oversight. A variety of opinions were expressed regarding the appropriate level of protocol review and oversight of clinical trials in the U.S. For example, the American Society of Transplant Surgeons stated that the Draft Guideline represented an unnecessary intrusion of government regulation into the performance of transplant surgery. In contrast, some organizations with commercial interests in the development of xenotransplantation contended that an inappropriate share of the burden for oversight of clinical trials had been assigned to local review committees and that the responsibility for this oversight should reside at the national level with the FDA. Several academic veterinarians, a group of 44 virologists, and other concerned citizens asserted that strict regulations should accompany the Guideline and that the major responsibility for determining the suitability of any animals as sources of nonhuman animal live cells, tissues or organs used in xenotransplantation must reside with the FDA.

The revised Guideline makes clear that, in addition to review by appropriate local review bodies (Institutional Review Boards, Institutional Animal Care and Use Committees, and the Institutional Biosafety Committees), the FDA has regulatory oversight for xenotransplantation clinical trials conducted in the U.S. Xenotransplantation products (i.e., live cells, tissues, or organs from a nonhuman animal source or human body fluids, cells, tissues, or organs that have had ex vivo contact with live cells, tissues, or organs from nonhuman animal sources and are used for xenotransplantation) are considered to be biological products, or combination products that contain a biological component, subject to regulation by FDA under section 351 of the Public Health Service Act (42 U.S.C. 262) and under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321 et seq.). In accordance with the applicable statutory provisions, xenotransplantation products are subject to the FDA regulations governing clinical investigations and product approvals (e.g., the Investigational new Drug [IND] regulations in 21 CFR Part 312, and the regulations governing licensing of biological products in 21 CFR Part 601). Investigators should submit an application for FDA review before proceeding with xenotransplantation clinical trials. Sponsors are strongly encouraged to meet with FDA staff in the pre-submission phase. In addition to the guidances referred to below, the FDA is considering further regulations and/or guidances regarding, for example, the development of xenotransplantation protocols

and the technical and clinical development of xenotransplantation products.

Xenotransplantation clinical protocols may also be reviewed by the Secretary's Advisory Committee on Xenotransplantation. The scope and process for this review will be described in future publications. [see revised guideline, sections 2.3, 5.3]

Responsibility for Design and Conduct of Clinical Protocols. The Draft Guideline originally proposed that clinical centers, source animal facilities, and individual investigators share the responsibilities for various aspects of the clinical trial protocol, including pre-xenotransplantation screening programs, patient informed consent procedures, record keeping, and post-xenotransplantation surveillance activities. The revised Guideline clarifies that primary responsibility for designing and monitoring the conduct of xenotransplantation clinical trials rests with the sponsor (as provided under, e.g., 21 CFR 312.23(a)(6)(d) and 312.50).

Informed Consent and Patient Education. Virologists, infectious disease specialists, health care workers, and patient advocates emphasized the need for the sponsor to offer assistance to xenotransplantation product recipients in educating their close contacts about potential infectious disease risks and methods for reducing those risks. The Guideline has been revised to state that the sponsor should ensure that counseling regarding behavior modification and other issues associated with risk of infection is provided to the patient and made available to the patient's family and other close contacts prior to and at the time of consent, and that such counseling should continue to be available thereafter. The revised Guideline clarifies and strengthens the informed consent process for xenotransplantation product recipients and the education and counseling process for recipients and their close contacts, including associated health care professionals. It also emphasizes the need for xenotransplantation product recipients to comply with long-term or life-long surveillance regardless of the outcome of the clinical trial or the status of the graft or other xenotransplantation product. [see revised guideline, sections 2.5.3, 2.5.4, 2.5.7.]

Deferral of Allograft and Blood Donors. The 1996 Draft Guideline recommended that xenotransplantation product recipients refrain from donating body fluids and/or parts for use in humans. Some infectious disease specialists and an infectious disease control practitioner organization suggested that this be strengthened to active deferral of xenotransplantation product recipients, and that consideration also be given to the deferral of close contacts of xenotransplantation product recipients. This issue was addressed by the FDA Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee (December, 1997, for transcript: http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3365t1.rtf). The committee recommended that xenotransplantation product recipients and their close contacts be counseled and actively deferred from donation of body fluids and other parts. A proposed FDA policy was then later presented to FDA's Blood Products Advisory Committee for further discussion, (March, 1998, for transcript: http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3391t2.rtf). Of note, at the time of both these

advisory committee meetings the operative definition of xenotransplantation did not include, as it does now, the use of certain products involving limited ex vivo exposure to xenogeneic cell lines or tissues. FDA has published a draft guidance document ("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") for public comment, which was again discussed by the FDA Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee on January 13, 2000. FDA will further consult with its advisors to identify the range of xenotransplantation products for which recipients and/or their contacts should be recommended for deferral from blood donation. Additionally, the range of contacts who should be deferred from blood donation will be clarified after further public discussion. The Guideline has been revised to reflect comments made at the FDA advisory committee meetings [see revised guideline, sections 2.5.11].

Xenotransplantation Product Sources. Strong opposition to the use of nonhuman primates as xenotransplantation product sources was voiced by many individuals and groups, including 44 virologists, scientific and medical organizations such as the American Society of Transplant Physicians, the American College of Cardiology, private citizens, and commercial sponsors of xenotransplantation clinical trials. The concerns focused on the ethics of using animals so closely related to humans, as well as the risk of transmission of infectious diseases from nonhuman primates to humans. Many recommended that the Guideline state that clinical xenotransplantation trials using xenotransplantation products for which nonhuman primates served as source animals should not occur until a closer examination of infectious disease risks can be adequately carried out.

Scientific findings since the publication of the Draft Guideline have also resulted in revisions. For example, the ability of simian foamy virus (SFV) to persistently infect human hosts has been further characterized [see revised guideline, section 6., references D.2.m. & D.4.d.], the persistence of microchimerism with anatomically dispersed baboon cells containing SFV, baboon cytomegalovirus (CMV), and baboon endogenous retrovirus (BaEV) in human recipients of baboon liver xenotransplantation products has been documented [see revised guideline, section 6., references D.3.a. & D.4.h.], and new viruses capable of infecting humans have been identified in pigs [see revised guideline, section 6., references D.2.a., b., f., g., h., i., v., w., x., bb., cc., ee., & gg.]. The active expression of infectious porcine endogenous retrovirus from multiple porcine cell types, and the ability of porcine endogenous retrovirus variants A and B to infect human cell lines in vitro has been demonstrated [see revised guideline, section 6., references D.1.q., s.; D.2.jj.; D.3.i.; D.4.a., e., f., m., s. & t.], giving scientific plausibility to concerns that this retrovirus from porcine xenotransplantation products may be able to infect recipients in vivo.

Diagnostic tests for porcine endogenous retrovirus, BaEV, and other relevant infectious agents have been developed [see revised guideline, section 6., references D.4.a., b., d., g., h., l., n., p., q., t. & u.] and studies are currently underway to assess the presence or absence of infectious endogenous

retroviruses and other relevant infectious agents in both porcine and baboon xenotransplantation products and in the recipients of these xenotransplantation products [see revised guideline, section 6., references D.3.a.; D.4.c., h., j., l. & n.]. The risk of endogenous retrovirus infection, however, is multi-factorial and it is not known whether results from these studies will be predictive of the potential infectious risks associated with future xenotransplantation products. One factor that impacts porcine endogenous retrovirus infectivity is its sensitivity to inactivation and lysis by human sera, yet the virus becomes resistant to inactivation after a single passage through human cells [see revised guideline, section 6., references D.2.jj. & D.4.m.]. It is hypothesized that pre-xenotransplantation removal of naturally occurring xenoreactive antibodies from the recipient and other modifications intended to facilitate xenotransplantation product survival, such as the procurement of xenotransplantation products or nonhuman animal live cells, tissues or organs used in the manufacture of xenotransplantation products from certain transgenic pigs, may also modulate the infectivity of endogenous retroviruses for xenotransplantation product recipients [see revised guideline, section 6., references D.1.d., o., q., s.; D.2.k., jj.; D.3.i.; D.4.e., k., m. & r.].

As the science regarding porcine endogenous retroviruses summarized above began to emerge, the FDA placed all clinical trials using porcine xenotransplantation products on hold (October 16, 1997) pending development by sponsors of sensitive and specific assays for (1) preclinical detection of infectious porcine endogenous retrovirus in porcine xenotransplantation products, (2) post-xenotransplantation screening for porcine endogenous retrovirus and clinical follow-up of porcine xenotransplantation product recipients, and (3) the development of informed consent documents that indicate the potential clinical implications of the capacity of porcine endogenous retrovirus to infect human cells in vitro. These issues were discussed publicly by the FDA Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee (December, 1997, for transcript: http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3365t1.rtf).

In response to concerns articulated by scientists and other members of the public regarding the use of nonhuman primate xenotransplantation products, the FDA, after consultation with other DHHS agencies, has issued a "Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans" containing the following conclusions:

> "...(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..."

While the document "Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans" specifically addresses the issue of nonhuman primates as sources for xenotransplantation products, the DHHS recognizes that other animal species have been used and/or are proposed as sources of xenotransplantation products and that all species pose infectious disease risks. Accordingly, the principles for source animal screening and health surveillance described in the revised Guideline apply to all candidate source animals regardless of species. These principles will need to be reassessed as new data become available.

Source Animal Screening and Qualification. Many groups and individuals expressed concern that the Draft Guideline did not set forth sufficiently stringent principles and criteria for source animal husbandry and screening, source animal facilities, and procurement and screening of xenotransplantation products. This view was expressed by virologists, veterinarians, infectious disease specialists, concerned citizens, commercial producers of laboratory animals, industrial sponsors of xenotransplantation trials, and a number of professional, scientific, medical, and advocacy organizations, such as the American Society of Transplant Surgeons, Doctors and Lawyers for Responsible Medicine, the American College of Cardiology, Biotechnology Industry Organization (BIO - representing 670 biotech companies), and the Association for Professionals in Infection Control and Epidemiology. Others expressed concern that the stringency of the Draft Guideline imposed high economic burdens on producers of xenotransplantation product source animals and/or on sponsors of xenotransplantation clinical trials. However, in order to reduce the potential public health risks posed by xenotransplantation, strict control of animal husbandry and health surveillance practices are needed during the course of development of this technology.

The Guideline has been revised to clarify the animal husbandry and pre-xenotransplantation infectious disease screening that should be performed before an animal can become a qualified source of xenotransplantation products. The revised Guideline now emphasizes that risk minimization precautions appropriate to each xenotransplantation product protocol should be employed during all steps of production and that screening, quarantine, and surveillance protocols should be tailored to the specific clinical protocol, xenotransplantation product, source animal and husbandry history. Breeding programs using cesarean derivation of animals should be used whenever possible. Source animals should be procured from closed herds or colonies raised in facilities that have appropriate barriers to effectively preclude the introduction or spread of infectious agents. These facilities should actively

monitor the herds for infectious agents. The revised Guideline clarifies and strengthens the infectious disease screening and surveillance practices that should be in place before a clinical trial can begin.

Specimen Archives and Medical Records. A number of infectious disease specialists, veterinarians, epidemiologists, industry sponsors of xenotransplantation trials, biotechnology companies, professional organizations such as the American Society of Transplant Physicians, and consumer advocates requested clarification regarding the collection and usage of, and access to, biological specimens obtained from both source animals and xenotransplantation product recipients.

The revised Guideline clarifies the recommended types, volumes, and collection schedule for biological specimens from both source animals and xenotransplantation product recipients. It also clearly distinguishes between biological specimens archived for public health investigations [see revised guideline, sections 4.1.2. and 3.7.] and specimens archived for use by the sponsor in conducting surveillance of source animals and post-xenotransplantation laboratory surveillance of xenotransplantation product recipients. The revised Guideline also states that health records and biologic specimens should be maintained for 50 years, based on the latency periods of known human pathogenic persistent viruses and the precedents established by the US Occupational Safety and Health Administration with respect to record-keeping requirements.

National Xenotransplantation Database. A number of infectious disease specialists, epidemiologists, transplant physicians, and a state health official emphasized the need for accurate and timely information on infectious disease surveillance and xenotransplantation protocols and their outcomes. They further supported the concept of a national xenotransplantation database as described in the Draft Guideline.

The revised Guideline describes the development of a pilot national xenotransplantation database to identify and implement routine data collection methods, system design, data reporting, and general start-up and to assess routine operational issues associated with a fully functional national database. The revisions also discuss plans to expand this pilot into a national xenotransplantation database intended to compile data from all clinical centers conducting trials in xenotransplantation and all animal facilities providing source animals for xenotransplantation.

Secretary's Advisory Committee on Xenotransplantation. Xenotransplantation research brings to the fore certain challenges in assessing the potential impact of science on society as a whole, including the role of the public in those assessments. The broad spectrum of public opinions expressed since the publication of the Draft Guideline indicates that there is neither uniform public endorsement nor rejection of xenotransplantation. The fields of research involved are rapidly moving ones, at the leading edge of medical science. Furthermore, in many instances the clinical trials are privately funded and the public may not even be aware of them. However, public awareness and understanding of xenotransplantation is vital because the potential infectious disease risks posed by xenotransplantation extend beyond the

individual patient to the public at large. In addition to these safety issues, a variety of individuals and groups have identified and/or raised concerns about issues such as animal welfare, human rights, community interest and consent, social equity in access to novel biotechnologies, and allocation of human allografts versus xenotransplantation products. For all of these reasons, public discourse on xenotransplantation research is critical and necessary.

The revised Guideline acknowledges the complexity, importance, and relevance of these issues, but emphasizes that the scope of the Guideline is limited to infectious disease issues. The revised Guideline discusses the development of the Secretary's Advisory Committee on Xenotransplantation (SACX) as a mechanism for ensuring ongoing discussions of the scientific, medical, social, and ethical issues and the public health concerns raised by xenotransplantation, including ongoing and proposed protocols. The SACX will make recommendations to the Secretary on policy and procedures and, as needed, on changes to the Guideline.

PHS GUIDELINE ON INFECTIOUS DISEASE ISSUES IN XENOTRANSPLANTATION

Table of Contents

1. Introduction

1.1. Applicability

This guideline was developed by the U.S. Public Health Service (PHS) to identify general principles of prevention and control of infectious diseases associated with xenotransplantation that may pose a hazard to public health. It is intended to provide general guidance to local review bodies evaluating proposed xenotransplantation clinical protocols and to sponsors in the development of xenotransplantation clinical protocols, in preparing submissions to FDA or the Secretary's Advisory Committee on Xenotransplantation (SACX, section 5.3.), and in the conduct of xenotransplantation clinical trials. Such clinical trials conducted within the United States are subject to regulation by the FDA under the Public Health Service Act (42 U.S.C. 262, 264), and the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.). This guidance document represents PHS's current thinking on certain infectious disease issues in xenotransplantation. It does not create or confer any rights for or on any person and does not operate to bind PHS or the public. This guidance is not intended to set forth an approach that addresses all of the potential health hazards related to infectious disease issues in xenotransplantation nor to establish the only way in which the public health hazards that are identified in this document may be addressed. The PHS acknowledges that not all of the recommendations set forth within this document may be fully relevant to all xenotransplantation products or xenotransplantation procedures. Sponsors of clinical xenotransplantation trials are advised to confer with relevant authorities (the FDA, other reviewing authorities, funding sources, etc) in assessing the relevance and appropriate adaptation of the general guidance offered here to specific clinical applications.

1.2. Definitions

This section defines terms as used in this guideline document.

1 Allograft - a graft consisting of live cells, tissues, and/or organs between individuals of the same species.

2 Closed herd or colony - herd or colony governed by Standard Operating Procedures that specify criteria restricting admission of new animals to assure that all introduced animals are at the same or a higher health standard compared to the residents of the herd or colony.

3 Commensal - an organism living on or within another, but not causing injury to the host.

4 Good Clinical Practices - A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

5 Infection Control Program - a systematic activity within a hospital or health care center charged with responsibility for the control and prevention of infections within the hospital or center.

6 Infectious agents - viruses, bacteria (including the rickettsiae), fungi, parasites, or agents responsible for Transmissible Spongiform Encephalopathies (currently thought to be prions) capable of invading and multiplying within the body.

7 Institutional Animal Care and Use Committee (IACUC) - a local institutional committee established to oversee the institution's animal program, facilities, and procedures. IACUC carry out semiannual program reviews and facility inspections and review all animal use protocols and any animal welfare concerns. (See PHS Policy on Humane Care and Use of Laboratory Animals, September 1986; reprinted March 1996).

8 Institutional Biosafety Committee (IBC) - A local institutional committee established to review and oversee basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment. (See Section IV-B-2 of the NIH Guidelines for Research Involving Recombinant DNA Molecules).

9 Institutional Review Board (IRB) - A local institutional committee established to review biomedical and behavioral research involving human subjects in order to protect the rights of human subjects (See 45 CFR Part 46, Protection of Human Subjects, and 21 CFR Part 56, Institutional Review Boards).

10 Investigator - an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug [or investigational product] is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team (see 21 CFR 312.3(b)).

11 Nosocomial infection - an infection acquired in a hospital.

12 Occupational Health Service - an office within a hospital or health care center charged with responsibility for the protection of workers from health hazards to which they may be exposed in the course of their job duties.

13 Procurement - the process of obtaining or acquiring animals or biological specimens (such as cells, tissues, or organs) from an animal or human for medicinal, research, or archival purposes.

14 Recipient – a person who receives or who undergoes ex vivo exposure to a xenotransplantation product (as defined in xenotransplantation).

15 Secretary's Advisory Committee on Xenotransplantation (SACX) - the advisory committee appointed by the Secretary of Health and Human Services to consider the full range of issues raised by xenotransplantation (including ongoing and proposed protocols) and make recommendations to the Secretary on policy and procedures.

16 Source animal - an animal from which cells, tissues, and/or organs for xenotransplantation are obtained.

17 Source animal facility - facility that provides source animals for use in xenotransplantation.

18 Sponsor - a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or a pharmaceutical company, government agency, academic institution, private organization or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator (see, e.g., 21 CFR 312.3(b)).

19 Transmissible spongiform encephalopathies (TSEs) - fatal, subacute, degenerative diseases of humans and animals with characteristic neuropathology (spongiform change and deposition of an abnormal form of a prion protein present in all mammalian brains). TSEs are experimentally transmissible by inoculation or ingestion of diseased tissue, especially central nervous system tissue. The prion protein (intimately associated with transmission and pathological progression) is hypothesized to be the agent of transmission. Alternatively, other unidentified co-factors or an as-yet unidentified viral agent may be necessary for transmission. Creutzfeldt-Jakob disease (CJD) is the most common human TSE.

20 Xenogeneic infectious agents - infectious agents that become capable of infecting humans due to the unique facilitating circumstances of xenotransplantation; includes

zoonotic infectious agents.

21 Xenotransplantation - for the purposes of this document, 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.

22 Xenotransplantation Product(s) - live cells, tissues or organs used in xenotransplantation (defined above). Previous PHS documents have used the term "xenograft" to refer to all xenotransplantation products.

23 Xenotransplantation Product Recipient - a person who receives or who undergoes ex vivo exposure to a xenotransplantation product.

24 Zoonosis - A disease of animals that may be transmitted to humans under natural conditions (e.g. brucellosis, rabies).

1.3. Background

The demand for human cells, tissues and organs for clinical transplantation continues to exceed the supply. The limited availability of human allografts, coupled with recent scientific and biotechnical advances, has prompted the renewed development of investigational therapeutic approaches that use xenotransplantation products in human recipients.

The experience with human allografts, however, has shown that infectious agents can be transmitted through transplantation. HIV/AIDS, Creutzfeldt-Jakob Disease, rabies, and hepatitis B and C, for example, have been transmitted between humans via allotransplantation. The use of live nonhuman cells, tissues and organs for xenotransplantation raises serious public health concerns about potential infection of xenotransplantation product recipients with both known and emerging infectious agents.

Zoonoses are infectious diseases of animals transmitted to humans via exposure to or consumption of the source animal. It is well documented that contact between humans and nonhuman animals -- such as that which occurs during husbandry, food production, or interactions with pets -- can lead to zoonotic infections. Many infectious agents responsible for zoonoses (e.g., Toxoplasma species, Salmonella species, or Cercopithecine herpesvirus 1 (B virus) of monkeys) are well characterized and can be identified through available diagnostic tests. Infectious disease public health concerns about xenotransplantation focus not only on the transmission of these known zoonoses, but also on the transmission of infectious agents as yet

unrecognized. The disruption of natural anatomical barriers and immunosuppression of the recipient increase the likelihood of interspecies transmission of xenogeneic infectious agents. An additional concern is that these xenogeneic infectious agents could be subsequently transmitted from the xenotransplantation product recipient to close contacts and then to other human beings. An infectious agent may pose risk to the patients and/or public if it can infect, cause disease in, and transmit among humans, or if its ability to infect, cause disease in, or transmit among humans remains inadequately defined.

Emerging infectious agents may not be readily identifiable with current techniques. This was the case with the several year delay in identifying HIV-1 as the etiologic agent for AIDS. Retroviruses and other persistent 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 diseases. As the HIV/AIDS pandemic demonstrates, persistent latent 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.

1.4. Scope of the Document

This guideline addresses the 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. While it is beyond the scope of this document to address the array of complex and important ethical issues raised by xenotransplantation, this guideline describes a mechanism for ensuring ongoing broad public discussion of ethical issues related to xenotransplantation (section 5.3). Other publications and reports of public discussions (section 6., references C.7.a., c., d., h., I.; D.1.b. & I.) have addressed issues such as animal welfare, human rights, and community interest.

This guideline reflects the status of the field of xenotransplantation and knowledge of the risk of xenogeneic infections at the time of publication. The general guidance in this document will be augmented by public discussion, new advances in scientific knowledge and clinical experience, and specific FDA guidance documents intended to facilitate the implementation of the principles set forth herein. HHS may ask the Secretary's Advisory Committee on Xenotransplantation (SACX) to review the Guideline on a periodic basis and recommend appropriate revisions to the Secretary (section 5.3).

1.5. Objectives

The objective of this PHS guideline is to present measures that can be used to minimize the risk of human disease due to xenogeneic infectious agents including both recognized zoonoses and non-zoonotic infectious agents that become capable of infecting humans due to the unique facilitating circumstances of xenotransplantation. In order to achieve this goal, this document:

- Outlines the composition and function of the xenotransplantation team to ensure that appropriate technical expertise can be applied (section 2.1).

- Addresses aspects of the clinical protocol, clinical center, and the informed consent and patient education processes with respect to public health concerns raised by the potential for infections associated with xenotransplantation (sections 2.2-2.5).

- Provides a framework for pre-transplantation animal source screening to minimize the potential for transmission of xenogeneic infectious agents from the xenotransplantation product to the human recipient (section 3, particularly sections 3.3-3.6).

- Provides a framework for post-xenotransplantation surveillance to monitor transmission of infectious agents, including newly identified xenogeneic agents, to the recipient as well as health care workers and other individuals in close contact with the recipient (section 4, particularly sections 4.1.1. and 4.2.3.).

- Provides a framework for hospital infection control practices to reduce the risk of nosocomial transmission of zoonotic and xenogeneic infectious agents (section 4.2.).

- Provides a framework for maintaining appropriate records, including human and veterinary health care records (section 4.3. and 3.7), standard operating procedures of facilities and centers (sections 3.2, 3.4), and occupational health service program records (section 4.3).

- Provides a framework for archiving biologic samples from the source animal and the xenotransplantation product recipient. These records and samples will be essential in the event that public health investigations are necessitated by infectious diseases and other adverse events arising from xenotransplantation that could affect the public health (sections 3.7, 4.1.2., and 5.2).

- Discusses the creation of a national database that will enable population based public health surveillance and investigation(s). (section 5.1).

- Discusses the creation of a Secretary's Advisory Committee on Xenotransplantation (SACX) that will consider the full range of complex and interrelated issues raised by xenotransplantation, including ongoing and proposed protocols (sections 2.3. and 5.3.).

2. Xenotransplantation Protocol Issues.

2.1. Xenotransplantation team.

The development and implementation of xenotransplantation clinical research protocols require expertise in the infectious diseases of both human recipients and source animals. Consequently, in addition to health care professionals who have clinical experience with transplantation, the xenotransplantation team should include as active participants:
(1) infectious disease physician(s) with expertise in zoonoses, transplantation, and epidemiology; (2) veterinarian(s) with expertise in the animal husbandry issues and infectious diseases relevant to the source animal; (3) specialist(s) in hospital epidemiology and infection control; and (4) experts in research and diagnostic microbiology laboratory methodologies. The sponsor should ensure that the appropriate expertise is available in the development and implementation of the clinical protocol, including the onsite follow up of the xenotransplantation product recipient.

2.2. Clinical Xenotransplantation Site

Any sites performing xenotransplantation clinical procedures should have experience and expertise with and facilities for any comparable allotransplantation procedures.

All xenotransplantation clinical centers should utilize CLIA'88 (Clinical Laboratory Improvements Act, amended in 1988) accredited virology and microbiology laboratories.

2.2.1. The safe conduct of xenotransplantation clinical trials should include the active participation of laboratories with the ability to isolate and identify unusual and/or newly recognized pathogens of both human and animal origin. Each protocol will present unique diagnostic, surveillance, and research needs that require expertise and experience in the microbiology and infectious diseases of both animals and humans. The sponsor should ensure that persons and centers with appropriate experience and expertise are involved in the study development, clinical application, and follow up of each protocol, either on-site or through formal and documented off-site collaborations.

2.3. Clinical Protocol Review

All clinical trials involving xenotransplantation are subject to regulation by the FDA under the

Public Health Service Act (42 U.S.C. 262, 264) and the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.).

Sponsors are responsible for ensuring reviews by local review bodies as appropriate, (Institutional Review Boards (IRBs), Institutional Animal Care and Use Committees (IACUCs), Institutional Biosafety Committees (IBCs)), the FDA, and the SACX (upon implementation by the Secretary, HHS). The scope and process for SACX review will be described in subsequent publications.

Institutional review of xenotransplantation clinical trial protocols should address: (1) the potential risks of infection for the recipient and contact populations (including health care providers, family members, friends, and the community at large); (2) the conditions of source animal husbandry (e.g., screening program, animal quarantine); and (3) issues related to human and veterinary infectious diseases (including virology, laboratory diagnostics, epidemiology, and risk assessment).

2.4. Health Screening and Surveillance Plans

Clearly defined methodologies for pre-xenotransplantation screening for known infectious agents and post-xenotransplantation surveillance are essential parts of clinical xenotransplantation trials and should be clearly developed in all protocols. Pre-xenotransplantation screening includes screening of the source herd (sections 3.2. - 3.4.), the source animal(s) (section 3.5.), and the nonhuman animal live cells, tissues or organs used in the manufacture of the xenotransplantation product or the product itself (section 3.6.). Post-xenotransplantation surveillance includes surveillance of the recipient(s) (section 4.1.), selected health care workers or other contacts (section 4.2.), and the surviving source animal(s) (section 3.6.). The screening methods used and the specific agents sought will differ depending on the procedure, cells, tissue, or organ used, the source animal, and the clinical indication for xenotransplantation. Details of these screening and surveillance plans, including 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) and written protocols for hospital infection control practices regarding both xenotransplantation product recipients and health care workers (section 4.2.) should be described in the materials submitted for review by the SACX, the FDA, and the local review bodies.

2.5. Informed Consent and Patient Education Processes

In the process of obtaining and documenting informed consent, the sponsor and investigators should comply with all applicable regulatory requirement(s) (e.g., Title 45 Code of Federal Regulations Part 46; Title 21 Code of Federal Regulations Parts 50 and 56), 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 and to recommendations from the National Bioethics Advisory Board (NBAC). The local IRB may consider having the consent process observed by a patient advocate (See e.g., 45 CFR 46.109(e)). In addition, the sponsor should ensure that counseling regarding behavior modification and other issues associated with risk of infection is provided to the patient and made available to the patient's family and contacts prior to and at the time of consent. Such counseling should remain available on an ongoing basis thereafter.

The informed consent discussion, the informed consent document, and the written information provided to potential xenotransplantation product recipients should address, at a minimum, the following points relating to the potential risk associated with xenotransplantation:

2.5.1. The potential for infection with zoonotic agents known to be associated with the nonhuman source animal species.

2.5.2. The potential for transmission to the recipient of unknown xenogeneic infectious agents. The patient should be informed of the uncertainty regarding the risk of infection, whether such infections might result in disease, the nature of disease that might result, and the possibility that infections with these agents may not be recognized for an extended period of time.

2.5.3. The potential risk for transmission of xenogeneic infectious agents (and possible subsequent manifestation of disease) to the recipient's family or close contacts, especially sexual contacts. The recipient should be informed that immunocompromised persons may be at increased risk of xenogeneic infections. The recipient should be counseled regarding behavioral modifications that diminish the likelihood of transmitting infectious agents and relevant infection control practices. (sections 4.2.1.1., 4.2.1.2., 4.2.1.5., and 4.2.3.1.).

2.5.4. The informed consent process should include a documented procedure to inform the recipient of the responsibility to educate his/her close contacts regarding the possibility 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 (e.g., unprotected sex, breast-feeding, 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 importance of reporting any significant unexplained illness through their health care provider to the research coordinator at the institutions where the xenotransplantation was performed.

2.5.5. The potential need for isolation procedures during any hospitalization (including to the extent possible the estimated duration of such confinement and the specific symptoms/situation that would prompt such isolation), and any specialized precautions needed to minimize acquisition or transmission of infections following hospital discharge.

2.5.6. The potential need for specific precautions following hospital discharge to minimize the risk that livestock of the source animal species and the recipient of the xenotransplantation product will represent biohazards to each other. For example, if a recipient comes into contact with the animal species from which the xenotransplantation product was procured, the xenotransplantation product (and therefore the recipient) may have an increased risk from exposures to agents infectious for the xenotransplantation product source species. Conversely, the recipient may represent a biohazard to healthy livestock if the presence of the xenotransplantation product enables the recipient to serve as a vector for outbreaks of disease in source species livestock.

2.5.7. The importance of complying with long-term or life-long surveillance necessitating routine physical evaluations and the archiving of tissue and/or body fluid specimens for public health purposes even if the experiment fails and the xenotransplantation product is rejected or removed. 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 immediately to the clinical investigator or his/her designee.

2.5.8. The responsibility of the xenotransplantation product recipient to inform the investigator or his/her designee of any change in address or telephone number for the purpose of enabling long-term health surveillance.

2.5.9. The importance of a complete autopsy upon the death of the xenotransplantation product recipient, even if the xenotransplantation product was previously rejected or removed. Advance discussion with the recipient and his/her family concerning the need to conduct an autopsy is also encouraged in order to ensure that the recipient's intent is known to all relevant parties.

2.5.10. The long term need for access by the appropriate public health agencies to the recipient’s medical records. To the extent permitted by applicable laws and/or regulations, the confidentiality of medical records should be maintained. The informed consent document should include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained (45 CFR 46.116 or 21 CFR 50.25(A)(5)).

2.5.11. As an interim precautionary measure, xenotransplantation product recipients and certain of their contacts should be deferred indefinitely from donation of Whole Blood, blood

components, including Source Plasma and Source Leukocytes, tissues, breast milk, ova, sperm, or any other body parts for use in humans. Pending further clarification, contacts to be deferred from donations should include persons who have engaged repeatedly in activities that could result in intimate exchange of body fluids with a xenotransplantation product recipient. For example, such contacts may include sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal, or other direct exposures. These recommendations may be revised based on ongoing surveillance of xenotransplantation product recipients and their contacts to clarify the actual risk of acquiring xenogeneic infections, and the outcome of deliberations between FDA and its advisors.

FDA has published a draft guidance document ("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") for public comment and will consult with its advisors to identify the range of xenotransplantation products for which recipients and/or certain of their contacts should be recommended for deferral from blood donation. Additionally, the range of contacts who should be deferred from blood donation will be clarified after further public discussion.

2.5.12. Xenotransplantation product recipients who may wish to consider reproduction in the future should be aware that a potential risk of transmission of xenogeneic infectious agents not only to their partner but also to their offspring during conception, embryonic/fetal development and/or breast-feeding cannot be excluded.

2.5.13. All centers where xenotransplantation procedures are performed should develop appropriate xenotransplantation procedure-specific educational materials to be used in educating and counseling both potential xenotransplantation product recipients and their contacts. These materials should describe the xenotransplantation procedure(s), and the known and potential risks of xenogeneic infections posed by the procedure(s) in appropriate language. Those activities that are considered to be associated with the greatest risk of transmission of infection to contacts should be described. Education programs should detail the circumstances under which the use of personal protective equipment (e.g., gloves, gowns, masks) or special infection control practices are recommended, and emphasize the importance of hand washing. The potential for transmission of these agents to the general public should be discussed.

3. Animal Sources for Xenotransplantation

Recognized zoonotic infectious agents and other organisms present in animals, such as normal flora or commensals, may cause disease in humans when introduced by xenotransplantation, especially in immunocompromised patients. The risk of transmitting xenogeneic infectious

agents is reduced by procuring source animals from herds or colonies that are screened and qualified as free of specific pathogenic infectious agents and that are maintained in an environment that reduces exposure to vectors of infectious agents. Precautions intended to reduce risk should be employed in all steps of production (e.g., during animal husbandry, procurement and processing of nonhuman animal live cells, tissues or organs used in the manufacture of xenotransplantation products) and should be appropriate to each xenotransplantation protocol. Before an animal species is used as a source of xenotransplantation product(s), sponsors should adequately address the public health issues raised. These issues are delineated in more detail below.

Procedures should be developed to identify incidents that negatively affect the health of the herd. This information is relevant to the safety review of every xenotransplantation product application. Such information, as well as the procedures to collect the information, should be reported to FDA.

Some experts consider that nonhuman primates pose a greater risk of transmitting infections to humans. The PHS recognized the substantial concerns about this issue that have been raised within the scientific community and the general public. In its April 6, 1999 guidance on nonhuman primate xenotransplantation products ("Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans"), FDA concluded, after consulting with other PHS agencies, that at the current time there is not sufficient information to assess the risks posed by nonhuman primate xenotransplantation. The FDA has determined that:

> "...(1) an appropriate federal advisory committee, such as the 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 FDA until sufficient scientific information exists addressing the risks posed by nonhuman primate xenotransplantation. 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..."

3.1. Animal Procurement Sources

All xenotransplantation products pose a risk of infection and disease to humans. Regardless of the species of the source animal, precautions appropriate to each xenotransplantation product protocol should be employed in all steps of production (animal husbandry, procurement and processing of nonhuman animal live cells, tissues or organs) to minimize this risk. Source animal procurement and processing procedures should include, at minimum, the following precautions:

3.1.1. Cells, tissues, and organs intended for use in xenotransplantation should be procured only from animals that have been bred and reared in captivity and that have a documented, well characterized health history and lineage.

3.1.2. Source animals should be raised in facilities with adequate barriers, i.e. biosecurity, to prevent the introduction or spread of infectious agents. Animals should also be obtained from herds or colonies with restricted admission of new animals. Such closed herds or colonies should be free of infectious agents that are relevant to the animal species and that may pose risk to the patient and/or the public. An infectious agent may pose risk to the patients and/or public if it can infect, cause disease in, and transmit among humans, or if its ability to infect, cause disease in, or transmit among humans remains inadequately defined. In this regard, persistent viral infections are of particular concern. Source animals should specifically be free of infection with any identifiable exogenous persistent virus. Breeding programs utilizing caesarean derivation of animals reduce the risk of maternal-fetal transmission of infectious agents and should be used whenever possible. The prevalence of exposure to these agents should be documented through periodic surveillance of the herd or colony using serologic and other appropriate diagnostic methodologies.

3.1.3. Animals from minimally controlled environments such as closed corrals (captive free-ranging animals) should not be used as source animals for xenotransplantation. Such animals have a higher likelihood of harboring adventitious infectious agents from uncontrolled contact with arthropods and/or other animal vectors.

3.1.4. Wild-caught animals should not be used as source animals for xenotransplantation.

3.1.5. Animals or live animal cells, tissues, or organs obtained from abattoirs should not be used for xenotransplantation. Such 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.

3.1.6. Imported animals or the first generation of offspring of imported animals should not be

used as source animals for xenotransplantation unless the animals belong to a species or strain (including transgenic animals) not available for use in the United States and their use is scientifically warranted. In this case, the imported animals should be documented to have been bred and continuously maintained in a manner consistent with the principles in this document. The source animal facility, production process and records are subject to inspection by the FDA (Federal Food, Drug and Cosmetic Act, [21 USC 374]). The US Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Veterinary Services (VS) regulates the importation of all animals and animal-origin materials that could represent a disease risk to U.S. livestock and poultry (9 CFR Part 122). Importation or interstate transport of any animal and/or animal-origin material that may represent such a disease risk requires a USDA permit. In addition, plans for testing and quarantine of the imported animals as well as health maintenance and surveillance of the herd or colony into which imported animals are introduced should be conducted by a veterinarian who is either specifically trained in or who otherwise has a solid background in foreign animal diseases.

3.1.7. Source animals from species in which transmissible spongiform encephalopathies have been reported should be obtained from closed herds with documented absence of dementing illnesses and controlled food sources for at least 2 generations prior to the source animal (section 3.2.6.3). Xenotransplantation products should not be obtained from source animals imported from any country or geographic region where transmissible spongiform encephalopathies are known to be present in the source species or from which the USDA prohibits or restricts importation of ruminants or ruminant products due to concern about transmissible spongiform encephalopathies.

3.1.8. The CDC, Division of Quarantine, regulates the importation of certain animals, including nonhuman primates (NHP), because of their potential to cause serious outbreaks of communicable disease in humans (42 CFR Part 71). Importers must register with CDC, certify imported NHP will be used only for scientific, educational, and exhibition purposes, implement disease control measures, maintain records regarding each shipment, and report suspected zoonotic illness in animals or workers.

Further, the importation and/or transfer of known or potential etiological agents, hosts, or vectors of human disease (including biological materials) may require a permit issued by CDC's Office of Health and Safety.

3.2. Source Animal Facilities

Potential source animals should be housed in facilities built and operated taking into account the factors outlined in this section.

3.2.1. Source Animal Facilities (facilities providing source animals for xenotransplantation) should be designed and maintained with adequate barriers to prevent the introduction and spread of infectious agents. Entry and exit of animals and humans should be controlled to minimize environmental exposures/inadvertent exposure to transmissible infectious agents. Source Animal Facilities should not be located in geographic proximity to manufacturing or agricultural activities that could compromise the biosecurity of these facilities.

3.2.2. Source Animal Facilities should have veterinarians on staff who possess expertise in the infectious diseases prevalent in the animal species and the emergency clinical care of the species. Facilities should also have persons with expertise in research virology and microbiology either on staff or as established consultants. These facilities should also maintain active and documented collaboration with accredited microbiology laboratories.

3.2.3. Procedures should be in place to assure the humane care of all animals (see e.g., the Animal Welfare Regulations as amended in 1985 (9 CFR Parts 1, 2, and 3) and the PHS Policy on the Humane Care and Use of Laboratory Animals).

3.2.4. Source Animal Facilities should incorporate procedures consistent with those set forth for accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) and should be consistent with the National Research Council's Guide for the Care and Use of Laboratory Animals (1996).

3.2.5. Source Animal Facilities should have a documented health surveillance system.

3.2.6. The Source Animal Facility standard operating procedures should thoroughly describe the following: (1) criteria for animal admission, including sourcing and entry procedures, (2) description of the disease monitoring program, (3) criteria for the isolation or elimination of diseased animals, including a diagnostic algorithm for ill and dead animals, (4) facility cleaning and disinfecting arrangements, (5) the source and delivery of feed, water and supplies, (6) measures to exclude arthropods and other animals, (7) animal transportation, (8) dead animal disposition, (9) criteria for the health screening and surveillance of humans entering the facility, and (10) permanent individual animal identification.

3.2.6.1. 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 replacement animals, the use of methods such as artificial insemination (AI), embryo transfer, medicated early weaning, cloning, or hysterotomy/hysterectomy and fostering may minimize further colonization with infectious agents.

3.2.6.2. During final screening and qualification of individual source animals and procurement of live cells, tissues or organs for use in xenotransplantation, the potential for transmission of an infectious agent should be minimized by established standard operating procedures. One method to accomplish this is 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, a cohort of qualified animals is quarantined from the closed herd or colony while undergoing final screening qualification and xenogeneic biomaterial procurement. After the entire cohort of source animals is removed, the quarantine and xenogeneic biomaterial processing areas of the animal facility are then cleaned and disinfected prior to the introduction of the next cohort of source animals.

3.2.6.3. The feed components, including any antibiotics or other medicinals or other additives, should be documented for a minimum of two generations prior to the source animal. Pasteurized milk products may be included in feeds. The absence of other mammalian materials, including recycled or rendered materials, should be specifically documented. The absence of such materials is important for the prevention of transmissible spongiform encephalopathies and 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 transmissible spongiform encephalopathies.

3.2.7. The sponsor should establish records linking each xenotransplantation product recipient with the relevant health history of the source animal, herd or colony, and the specific organ, tissue, or cell type included in the xenotransplantation product or used in the manufacture of the xenotransplantation product. The relevant records include information on the standard operating procedures of the animal procurement facility, the herd health surveillance, and the lifelong health history of the source animal(s) for the xenotransplantation product (sections 3.2. - 3.7.).

3.2.7.1. The sponsor should maintain these record systems and an animal numbering or other system that allows easy, accurate, and rapid linkage between the information contained in these different record systems and the xenotransplantation product recipient for 50 years beyond the date of xenotransplantation. If record systems are maintained in a computer database, electronic back ups should be kept in a secure office facility and back up on hard copy should be routinely performed.

3.2.7.2. In the event that the Source Animal Facility ceases to operate, the facility should either transfer all animal health records and specimens to the respective sponsors or notify the sponsors of the new archive site. If the sponsor ceases to exist, decisions on the disposition of the archived records and specimens should be made in consultation with the FDA.

3.2.8. All animal facilities should be subject to inspection by designated representatives of the clinical protocol sponsor and public health agencies. The sponsor is responsible for implementing and maintaining a routine facilities inspection program for quality control and quality assurance.

3.3. Pre-xenotransplantation 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 nonhuman animal live cells, tissues or organs used in xenotransplantation. The selection of assays for pre-transplant screening should be determined by the source of the nonhuman animal live cells, tissues or organs and the intended clinical application of the xenotransplantation product. General guidance on adventitious agent testing may be found in 'Points to Consider for the Characterization of Cell Lines Used to Produce Biologicals'(FDA, CBER, 1993), and a guidance document from the International Conference on Harmonization: 'Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Subsets Used for Production of Biotechnological/Biological Products'.

3.3.1. The design of preclinical studies intended to identify infectious agents in the xenotransplantation product and/or the nonhuman animal live cells, tissues or organs intended for use in the manufacture of xenotransplantation products should take into consideration the source animal species and the specific manner in which the xenotransplantation product will be used clinically. These studies should identify infectious agents and characterize their potential pathogenicity and tropism for human cells by appropriate in vivo and in vitro assays. Characterization of persistent viral infections and endogenous retroviruses present in source animals cells, tissues or organs is particularly important. The information from these studies is necessary for the identification and development of appropriate assays for xenotransplantation product screening programs.

3.3.2. Programs for screening and detection of known infectious agents in the herd or colony, the individual source animal, and the xenotransplantation product itself or the nonhuman animal live cells, tissues or organs used in the manufacture of xenotransplantation products should take into account the infectious agents associated with the source animals used, the stringency of the husbandry techniques employed, and the manner in which the xenotransplantation product will be used clinically. These programs should be updated periodically to reflect advances in the knowledge of infectious diseases. The sponsor should develop an adequate screening program in consultation with appropriate experts including oversight and regulatory bodies.

3.3.3. Assays used for screening and detection of infectious agents should have well defined and documented sensitivity, specificity, and reproducibility in the setting in which they are employed. In addition to assays for specific infectious agents, the use of assays capable of

detecting broad ranges of infectious agents is strongly encouraged. In vivo assays involving animal models may require different standards for evaluation. Assays under development may complement the screening process.

3.3.4. Samples from the xenotransplantation product itself or of the nonhuman animal live cells, tissues or organs used in the manufacture of the xenotransplantation product, whenever possible, or from an appropriate biologic proxy should be tested preclinically with co-cultivation assays. These assays should include a panel of appropriate indicator cells, which may include human peripheral blood mononuclear cells (PBMC), to facilitate amplification and detection of endogenous retroviruses and other xenogeneic viruses capable of producing infection in humans. Agents that may be latent are of particular concern and their detection may be facilitated by using chemical and irradiation methods.

3.3.5. All xenotransplantation products should be screened by direct culture for bacteria, fungi, and mycoplasma (see, e.g., 21 CFR Part 600-680). In addition, universal PCR probes for the presence of micro-organisms are available and should be considered to complement the screening of xenotransplantation products.

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 of stock (optimally caesarian derived) raised in barrier facilities; and (2) adequate surveillance programs for infectious agents. The standard operating procedures of the animal facility with regard to the herd or colony health maintenance and surveillance programs relevant to the specific xenotransplantation product usage should be documented and available to appropriate review bodies. Medical records for the herd or colony and the specific individual source animals should be maintained by the animal facility or the sponsor, as appropriate, for 50 years beyond the date of the xenotransplantation.

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 and taken into account when interpreting serologic screening tests. Prevention of disease by protection from exposure is generally preferable to vaccination, since this preserves the ability of serologic screening to define herd exposures. In particular, the use of live vaccines is discouraged, but may be justified when dead or acellular vaccines are not

available and barriers to exposure are inadequate to prevent the introduction of infectious agents into the herd or colony.

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 sponsor should describe the monitoring program, including the types and schedules of physical examinations and laboratory tests used in the detection of all infectious agents, and document the results.

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. Since 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. The geographic origin of the founding stock of the colony, including quarantine and screening procedures utilized when the closed colony was established, should be taken into consideration. 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 indicators of infectious agents relevant to the species and epidemiologic exposures. Additional directed serologic analysis, active culturing, or other diagnostic laboratory testing 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. Aliquots of serum samples collected during routine surveillance and specific disease investigations should be maintained for 50 years beyond the date of sample collection. The Source Animal Facility or the sponsor should maintain these specimens (either on- or off-site) for investigations of unexpected diseases that occur in the herd, colony, individual source animals, or animal facility staff. These herd health surveillance samples, which are not archived for PHS investigation purposes, should nonetheless be made available to the PHS if needed. (section 3.7.)

3.4.3.2. Any animal deaths, including stillbirths or abortions, where the cause is either unknown or ambiguous should lead to full necropsy and evaluation for infectious etiologies (including transmissible spongiform encephalopathies) by a trained veterinary pathologist. Results of these investigations should be documented.

3.4.4. Standard operating procedures that include maintenance of a subset of sentinel animals

are encouraged. Monitoring of these animals will increase the probability of detection of subclinical, latent, or late-onset diseases such as transmissible spongiform encephalopathies.

3.5. Individual Source Animal Screening and Qualification

The qualification of individual source animals should include documentation of breed and lineage, general health, and vaccination history, particularly the use of live and/or live attenuated vaccines (section 3.4.1). The presence of pathogens that result in acute infections should be documented and controlled by clinical examination and treatment of individual source animals, by use of 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. The use of any drugs or biologic agents for treatment should be documented. During quarantine and/or prior to procurement of live cells, tissues or organs for use in xenotransplantation, individual source animals should be screened for infectious agents relevant to the particular intended clinical use of the planned xenotransplantation product. The screening program should be guided by the surveillance and health history of the herd or colony.

3.5.1. In general, individual source animals should be quarantined for 3 weeks prior to procurement of live cells, tissues or organs for use in xenotransplantation. During the quarantine, 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 the need for and duration of individual quarantine periods depending on the characterization and surveillance of the source animal herd or colony, the design of the facility in which the herd is bred and maintained, and the clinical urgency. When the quarantine period is shortened or eliminated, justification should be documented and any potentially increased infectious risk should be addressed in the informed consent document.

3.5.1.1. During the quarantine period, candidate source animals should be examined by a veterinarian and screened for the presence of infectious agents (bacteria including rickettsiae when appropriate, parasites, fungi, and viruses) by appropriate serologies and cultures, serum clinical chemistries (including those specific to the function of the organ or tissue to be procured), complete blood count and peripheral blood smear, and fecal exam for parasites. Evaluation for viruses which may not be recognized zoonotic agents but which have been documented to infect either human or nonhuman 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. Surveillance of a closed herd or colony (as described in section 3.4.3.) will minimize the additional screening necessary to qualify individual member animals. The nature, timing, and results of surveillance of the herd or colony from which the individual animal is procured should be considered in designing appropriate additional

screening of individual animals. These tests should be performed as closely as possible to the date of xenotransplantation while ensuring availability of results prior to clinical use.

3.5.1.2. Screening of a candidate source animal should be repeated prior to procurement of live cells, tissues or organs for use in xenotransplantation if a period greater than three months has elapsed since the initial screening and qualification were performed or if the animal has been in contact with other non-quarantined 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 microbiologic protection ensured by the closed colony. Careful attention to conditions of transport can minimize disease exposures during shipping. Microbiological isolation of the source animal during transit is critically important. Source animals should be transported using a system that reliably ensures microbiological isolation. Transported source animals should be quarantined for a minimum period of three weeks after transportation, during which time appropriate screening should be performed. The sponsor may propose a shorter quarantine period if appropriate justification (that reflects the level of containment and the duration of the transportation) is provided. When source animals are transported intact, the sponsor should consult the FDA about further details of appropriate transport, quarantine, and screening. If the animals are transported across state or federal boundaries the USDA should be consulted.

3.5.1.4. For the reasons cited above, it is preferable, whenever feasible, to procure live cells, tissues or organs for use in xenotransplantation at the animal facility. Precautions employed during transport to ensure microbiological isolation of the procured xenotransplantation product or live cells, tissues or organs should be documented.

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

3.5.3. When feasible a biopsy of the nonhuman animal live cells, tissues or organs intended for use in xenotransplantation, the xenotransplantation product itself, or other relevant tissue should be evaluated for the presence of infectious agents by appropriate assays and histopathology prior to xenotransplantation, and then archived (section 3.7).

3.5.4. The sponsor should ensure that the linked records described in section 3.2.7. are available for review when appropriate by the local review bodies, the SACX, and the FDA.

These records should include information on the results of the quarantine and screening of individual xenotransplantation source animals. In addition to records kept at the Source Animal Facility, a summary of the individual source animal record should accompany the xenotransplantation product and be archived as part of the medical record of the xenotransplantation product recipient.

3.5.5. The Source Animal Facility should notify the sponsor in the event that an infectious agent is identified in the source animal or herd subsequent to procurement of live cells, tissues or organs for use in xenotransplantation (e.g., identification of delayed onset transmissible spongiform encephalopathies in a sentinel animal).

3.5.6. The sponsor should ensure that the quarantine, screening, and qualification program is appropriately tailored to the specific source animal species, the animal husbandry history, the process for procuring the xenogeneic biomaterial and preparing the xenotransplantation product, and the clinical application. The sponsor should also ensure that the results of these procedures are reviewed and approved by persons with the appropriate expertise prior to the clinical application.

3.6. Procurement and Screening of Nonhuman Animal Live Cells, Tissues or Organs Used for Xenotransplantation

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 may be subject to inspection by appropriate oversight and regulatory authorities.

3.6.2. Cells, tissues or organs intended for xenotransplantation that are maintained in culture prior to xenotransplantation should be periodically screened for maintenance of sterility, including screening for viruses and mycoplasma. The FDA publications titled "Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (1998)"; "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. The sponsor should develop, implement, and stringently enforce the standard operating procedures for the procurement and screening processes. Procedures that may inactivate or remove pathogens without compromising the integrity and function of the xenotransplantation product should be employed.

3.6.3. All steps involved in the procuring, processing, and screening of live cells, tissues or organs or xenotransplantation products to the point of xenotransplantation should be rehearsed

preclinically to ensure reproducible quality control.

3.6.4. If nonhuman animal live cells, tissues or organs for use in xenotransplantation are procured without euthanatizing the source animal, the designated PHS specimens should be archived (PHS specimens are discussed in section 3.7.1.) and the animal's health should be monitored for life. When source animals die or are euthanatized, a complete necropsy with gross, histopathologic and microbiological evaluation by a trained veterinary pathologist should follow, regardless of the time elapsed between xenogeneic biomaterial procurement and death. This should include evaluation for transmissible spongiform encephalopathies. The sponsor should maintain documentation of all necropsy results for 50 years beyond the date of necropsy as part of the animal health record (sections 3.2.7. and 3.4.). In the event that the necropsy reveals findings pertinent to the health of the xenotransplantation product recipient(s) (e.g., evidence of transmissible spongiform encephalopathies) the finding should be communicated to the FDA without delay (see e.g., 21 CFR 312.32).

3.7. Archives of Source Animal Medical Records and Specimens

Systematically archived source animal biologic samples and record keeping that allows rapid and accurate linking of xenotransplantation product 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. Source animal biologic specimens designated for PHS use (as outlined below) should be banked at the time of xenogeneic biomaterial procurement. These specimens should remain in archival storage for 50 years beyond the date of the xenotransplantation to permit retrospective analyses if a public health need arises. Such archived specimens should be readily accessible to the PHS and remain linked to both source animal and recipient health records.

At the time of procurement of nonhuman animal live cells, tissues or organs for use in xenotransplantation, plasma should be collected from the source animal and stored in sufficient quantity for subsequent serology and viral testing. In addition, the sponsor should recover and bank sufficient aliquots of cryopreserved leukocytes for subsequent isolation of nucleic acids and proteins as well as aliquots for thawing viable cells for viral co-culture assays or other tissue culture assays. Ideally at least ten 0.5 cc aliquots of citrated or EDTA-anticoagulated plasma should be banked. At least five aliquots of viable ($1x10^7$) leukocytes should be cryopreserved. It may also be appropriate to collect paraffin-embedded, formalin fixed, and cryopreserved tissue samples from source animal organs relevant to the specific protocol at the time of xenogeneic biomaterial procurement. Additionally, cryopreserved tissue samples representative of major organ systems (e.g., spleen, liver, bone marrow, central nervous system, lung,) should be collected from source animals at necropsy. The material submitted for review by FDA and,

when appropriate, the Secretary's Advisory Committee on Xenotransplantation (under development, see section 5.3) should justify the types of tissues, cells, and plasma taken for storage and any smaller quantities of plasma and leukocytes collected.

3.7.2. The sponsor should maintain archives of designated PHS specimens (section 3.7.1.) and serum collected for herd surveillance for 50 years beyond the date of collection (section 3.4.3.1.), and animal health records for 50 years beyond the date of the animal's death (sections 3.2.7.).

3.8. Disposal of Animals and Animal By-products

The need for advanced planning for the ultimate disposition of source and sentinel animals bred for xenotransplantation, especially animals of species ordinarily used to produce food, should be anticipated. Generally source and sentinel animals should not be used as pets, breeding animals, sources of human food via milk or meat, or as ingredients of feed for other animals because of their potential to enter the human or animal food chain.

3.8.1. There may be species specific situations where animals from xenotransplant facilities can be considered to be safe for human food use or as feed ingredients when disposed of through rendering. FDA's Center for Veterinary Medicine (CVM) regulates animal feed ingredients and also establishes conditions for the release of animals to the USDA Food Safety Inspection Service for inspection as food for humans. Persons wishing to offer animals into the human food or animal feed supply or who have food safety questions should consult with CVM. Food safety issues will be referred to CVM.

3.8.2. Animals from biomedical facilities that have not been authorized for release by CVM into the human food or animal feed supply may be adulterated under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321 et seq.), unfit for food or feed, and potentially infectious. They should be disposed of in a manner consistent with infectious medical waste in compliance with federal, state and local requirements.

4. Clinical Issues

4.1. Xenotransplantation Product Recipient

4.1.1. Surveillance of the xenotransplantation product recipient

Post-xenotransplantation clinical and laboratory surveillance of xenotransplantation product recipients is critical, as it provides the means of monitoring for any introduction and propagation of xenogeneic infectious agents in the xenotransplantation product recipient. The sponsor should

carry out, and ensure documentation of, the surveillance program. Life-long post-xenotransplantation surveillance of xenotransplantation product recipients is appropriate.

4.1.1.1. Recipients should be evaluated throughout their lifetime for adverse clinical events potentially associated with xenogeneic infections.

4.1.1.2. Laboratory surveillance of the xenotransplantation product recipient should be instituted when xenogeneic infectious agents are known or suspected to be present in the xenotransplantation product. Minimally, laboratory surveillance should be conducted for evidence of recipient infection with all identified xenotropic endogenous retroviruses known to be present in the source animal. The intent of active screening in this setting is detection of sentinel human infections prior to dissemination in the general population. Serum, PBMCs, tissue or other body fluids should be assayed at intervals post-xenotransplantation for xenogeneic agents known or suspected to be present in the xenotransplantation product. Laboratory surveillance should include frequent screening in the immediate post-xenotransplantation period (e.g., at 2, 4, and 6 weeks after xenotransplantation) that decreases in frequency if evidence of infection remains absent.

It is critical that adequate diagnostic assays and methodologies for surveillance of known infectious agents from the source animal are available prior to initiating the clinical trial. The sensitivity, specificity, and reproducibility of these testing methods should be documented under conditions that simulate those employed at the time of and following the xenotransplantation procedure. As with pre-xenotransplantation screening, assays under development may complement the surveillance process (see section 3.3.3.).

The laboratory surveillance should include methods to detect infectious agents known to establish persistent latent infections in the absence of clinical symptoms (e.g., herpesviruses, retroviruses, papillomaviruses) and that are known or suspected to have been present in the xenotransplantation product. When the xenogeneic viruses of concern have similar human counterparts (e.g., simian cytomegalovirus), assays to distinguish between the two should be used in the post-xenotransplantation laboratory surveillance. Depending upon the degree of immunosuppression in the recipient, serological assays may be or may not be useful. Methods for analysis may include co-cultivation of cells coupled with appropriate detection assays.

4.1.2. Xenotransplantation Product Recipients' Biologic Specimens Archived for Public Health Investigations (PHS Specimens).

Biological specimens obtained from the xenotransplantation product recipients and designated for public health investigations (as distinct from specimens collected for clinical evaluation or laboratory surveillance) should be archived for 50 years beyond the date of the

xenotransplantation to allow retrospective investigation of xenogeneic infections. The type and quantity of specimens archived may vary with the clinical procedure and the age of the xenotransplantation product recipient. In the application for FDA review, which may also be reviewed by the SACX, the sponsor should justify the amount and types of specimens to be designated for PHS use, including any differences from the recommendations described below.

At selected time points, at least three to five 0.5 cc aliquots of citrated or EDTA-anticoagulated plasma should be recovered and archived. At least two aliquots of viable (1×10^7) leukocytes should be cryopreserved. Specimens from any xenotransplantation product that is removed (e.g., post-rejection or at the time of death) should be archived.

The following schedule for archiving biological specimens is recommended: (1) Prior to the xenotransplantation procedure, 2 sets of samples should be collected and archived one month apart. If this is not feasible then two sets should be collected and archived at times that are separated as much as possible. One set should be collected immediately prior to the xenotransplantation. (2) Additional sets should be archived in the immediate post-xenotransplantation period and at approximately one month and six months after xenotransplantation. (3) Collection should then be obtained annually for the first two years after xenotransplantation. (4) After that, specimens should be archived every five 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.

4.1.2.1. In the event of recipient's death, snap-frozen samples stored at -70^o C, paraffin embedded tissue, and tissue suitable for electron microscopy should be collected at autopsy from the xenotransplantation product and all major organs relevant to either the xenotransplantation or the clinical syndrome that resulted in the patient's death. These designated PHS specimens should be archived for 50 years beyond the date of collection.

4.1.2.2. The sponsor should maintain an accurate archive of the PHS specimens. In the absence of a central facility (section 5.2), these specimens should be archived with the safeguards necessary 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.

The sponsor should maintain these archives and a record system that allows easy, accurate, and rapid linkage of information among the different record systems (i.e., the specimen archive, the recipient's medical records and the records of the source animal) for 50 years beyond the date of xenotransplantation. If record systems are maintained in a computer database, electronic back ups should be kept in a secure office facility and back up on hard copy should be routinely performed.

4.1.2.3. A clinical episode potentially representing a xenogeneic infection should prompt notification of the FDA, which will notify other federal and state health authorities as appropriate. Under these circumstances, the PHS may decide that an investigation involving the use of these archived biologic specimens is warranted to assess the public health significance of the infection.

4.2. Infection Control

4.2.1. Infection control practices

4.2.1.1. Strict adherence to recommended infection control measures will reduce the risk of transmission of xenogeneic infections and other blood borne and nosocomial pathogens. Standard Precautions should be used for the care of all patients. Standard Precautions includes hand washing before and after each patient contact, appropriate use of barriers, and care in the use and disposal of needles and other sharp instruments.

4.2.1.2. 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 xenotransplantation team infectious disease specialist. For example, appropriate isolation precautions for each hospitalized xenotransplantation product recipient will depend upon the type of xenotransplantation, the extent of immunosuppression, and patient symptoms. Isolation precautions should be continued until a diagnosis has been established or the patient symptoms have resolved. The appropriateness of isolation precautions and other infection control measures should be reassessed when the diagnosis is established, the patient's symptoms change, and at the time of readmission and discharge. Discharge instructions should include specific education on appropriate infection control practices following discharge, including any special precautions recommended for disposal of biologic products. The most restrictive level of isolation
should be used when patients exhibit respiratory symptoms because airborne transmission of infectious agents is most concerning.

4.2.1.3. Health care personnel, including xenotransplantation team members, should adhere to recommended procedures for handling and disinfection/sterilization of medical instruments and disposal of infectious waste.

4.2.1.4. Biosafety level 2 (BSL-2) standard and special practices, containment equipment and facilities should be used for activities involving clinical specimens from xenotransplantation product recipients. Particular attention should be given to sharps management and bioaerosol containment. BSL-3 standard and special practices and containment equipment should be employed in a BSL-2 facility when propagating an unidentified infectious agent isolated from a

xenotransplantation product recipient.

4.2.2. Acute Infectious Episodes

Most acute viral infectious episodes among the general population are never etiologically identified. Xenotransplantation product recipients are at risk for these infections and other infections common among immunosuppressed allograft recipients. When the source of an illness in a recipient remains unidentified despite standard diagnostic procedures, it may be appropriate to perform additional testing of body fluid and tissue samples. The infectious disease specialist, in consultation with the hospital epidemiologist, the veterinarian, the clinical microbiologist and other members of the xenotransplantation team should assess each clinical episode and make a considered judgment regarding the significance of the illness, the need and type of diagnostic testing and specific infection control precautions. Other experts on infectious diseases and public health may also need to be consulted.

4.2.2.1. In immunosuppressed xenotransplantation product recipients, assays of antibody response may not detect infections reliably. In such patients, culture systems, genomic detection methodologies and other techniques may detect infections 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 either on site or through active and documented collaborations. Specimens should be handled to ensure 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.

4.2.2.2. Acute and convalescent sera obtained in association with acute unexplained illnesses should be archived when judged appropriate by the infectious disease physician and/or the hospital epidemiologist. This would permit retrospective study and perhaps the identification of an etiologic agent.

4.2.3. Health Care Workers

The risk to health care workers who provide post-xenotransplantation care to xenotransplantation product recipients is undefined. However, health care workers, including laboratory personnel, who handle the animal tissues/organs prior to xenotransplantation 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.

The sponsor should ensure that a comprehensive Occupational Health Services program is available to educate workers regarding the risks associated with xenotransplantation and to monitor for possible infections in workers. The Occupational Health Service program should include:

4.2.3.1. Education of Health Care Workers

All centers where xenotransplantation procedures are performed should develop appropriate xenotransplantation procedure-specific educational materials for their staff. These materials should describe the xenotransplantation procedure(s), the known and potential risks of xenogeneic infections posed by the procedure(s), and research or health care activities that may pose the greatest risk of infection or nosocomial transmission of zoonotic or other infectious agents. Education programs should detail the circumstances under which the use of Standard Precautions and other isolation precautions are recommended, including the use of personal protective equipment handwashing before and after all patient contacts, even if gloves are worn. In addition, the potential for transmission of these agents to the general public should be discussed.

4.2.3.2. Health Care Worker Surveillance

The sponsor and the Occupational Health Service in each clinical center should develop protocols for monitoring health care personnel. These protocols should describe methods for storage and retrieval of personnel records and collection of serologic specimens from workers. Baseline sera (i.e., prior to exposure to xenotransplantation products or recipients) should be collected from all personnel who provide direct care to xenotransplantation product recipients, and laboratory personnel who handle, or are likely to handle, animal cells, tissues and organs or biologic specimens from xenotransplantation product recipients. Baseline sera can be compared to sera collected following occupational exposures; such baseline sera should be maintained for 50 years from the time of collection. The activities of the Occupational Health Service should be coordinated with the Infection Control Program to ensure appropriate surveillance of infections in personnel.

4.2.3.3. Post-Exposure 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 needle stick. Health care workers, including laboratory personnel, should be instructed to report exposures immediately to the Occupational Health Services. The post-exposure 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, post-exposure management, and follow-up) and the outcome of the event. This information should be archived in a health exposure log (section 4.3.) and maintained for at least 50 years from the time of the xenotransplantation 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.

4.3. Health Care Records

The sponsor should maintain a cross-referenced system that links the relevant records of the xenotransplantation product recipient, xenotransplantation product, source animal(s), animal procurement center, and significant nosocomial exposures. These records should include: (1) documentation of each xenotransplantation procedure, (2) documentation of significant nosocomial health exposures, and (3) documentation of the infectious disease screening and surveillance records on both xenotransplantation product source animals and recipients. These records should be updated regularly and cross-referenced to allow rapid and easy linkage between the clinical records of the source animal(s) and the xenotransplantation product recipient.

To the extent permitted by applicable laws and/or regulations, the confidentiality of all medical and research records pertaining to human recipients should be maintained (section 2.5.10.).

4.3.1. The documentation of each xenotransplantation procedure includes the date and type of the procedure, the principal investigator(s) (PI), the xenotransplantation product recipient, the xenotransplantation product(s), the individual source animal(s) and the procurement facilities for these animals, as well as the health care workers associated with each procedure.

4.3.2. The documentation of significant nosocomial health exposures includes the persons involved, the date and nature of each potentially significant nosocomial exposure (exposures defined in the written Infection Control/Occupational Health Service protocol), and the actions taken.

4.3.3. The documentation of infectious disease screening and surveillance includes: (a) a summary of the source animal(s) health status; (b) the results of the pre-xenotransplantation screening program for the source animal(s); (c) the results of the pre-xenotransplantation screening program for the xenotransplantation product; (d) the post-xenotransplantation surveillance studies on the xenotransplantation product recipient; and (e) a summary of significant relevant post-xenotransplantation clinical events.

5. Public Health Needs

5.1. National Xenotransplantation Database

A pilot project to demonstrate the feasibility of, and identify system requirements for, a National Xenotransplantation Database is currently underway. It is anticipated that this pilot would be expanded into a fully operational Database to collect data from all clinical centers conducting trials in xenotransplantation and all animal facilities providing animals or xenogeneic organs, tissues, or cells for clinical use. Such a database would enable: (a) the recognition of rates of occurrence and clustering of adverse health events, including events that may represent outcomes of xenogeneic infections; (b) accurate linkage of these events to exposures on a national level; (c) notification of individuals and clinical centers regarding epidemiologically significant adverse events associated with xenotransplantation; and (d) biological and clinical research assessments. When such a Database becomes functional, the sponsor should ensure that information requested by the Database is provided in an accurate and timely manner. To the extent allowed by law, information derived from the Database would be available to the public with appropriate confidentiality protections for any proprietary or individually identifiable information.

5.2. Biologic Specimen Archives

The sponsor should ensure that the designated PHS specimens from the source animals, xenotransplantation products, and xenotransplantation product recipients are archived (sections 3.7.1, 3.5.3, and 4.1.2.). The biologic specimens should be collected and archived under conditions that will ensure their suitability for subsequent public health purposes, including public health investigations (sections 4.1.2.3.). The location and nature of archived specimens should be documented in the health care records and this information should be linked to the National Xenotransplantation Database when the latter becomes functional.

DHHS is considering options for a central biological archive, e.g., one maintained by a private sector organization under contract to DHHS. Designated PHS specimens would be deposited in such a repository.

5.3. Secretary's Advisory Committee on Xenotransplantation (SACX)

The SACX is currently being implemented by DHHS. As currently envisioned, the SACX will consider the full range of complex issues raised by xenotransplantation, including ongoing and proposed protocols, and make recommendations to the Secretary on policy and procedures. The SACX will also provide a forum for public discussion of issues when appropriate. These activities will facilitate DHHS efforts to develop an integrated approach to addressing emerging

public health issues in xenotransplantation. The structure and functions of the SACX as well as procedures for SACX review of protocols and issues will be described in subsequent publications. Inquiries about the status and function of, and access to the SACX should be directed to the Office of Science Policy, Office of the Secretary, DHHS, or the Office of Biotechnology Activities (OBA), formerly known as the Office of Recombinant DNA Activities (ORDA), Office of the Director, NIH.

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[Please note that the documents identified with an asterisk "*" can 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. In addition, documents marked with two asterisks "**" can be found on the internet at the indicated websites.]

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