

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 Intimate Contacts

DRAFT GUIDANCE

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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 Intimate Contacts

This guidance document represents the agency's current thinking on precautionary measures to reduce the possible risk of transmission of zoonoses by blood and blood products from xenotransplantation product recipients and their intimate contacts. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance document notifies you, all registered blood and plasma establishments, and establishments engaged in manufacturing plasma derivatives, of the Food and Drug Administration's (FDA) recommendations to indefinitely defer xenotransplantation product recipients and their intimate contacts from donating blood or plasma. This document also contains recommendations regarding the disposition of blood products manufactured from a donor who is retrospectively discovered to have received a xenotransplantation product or to have been an intimate contact of a xenotransplantation product recipient.

II. DEFINITIONS

The following terms are defined for the purpose of this document.

- Xenotransplantation is 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,

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- Xenotransplantation products include live cells, tissues or organs used in xenotransplantation. Biological products, drugs, or medical devices sourced from nonliving cells, tissues or organs from nonhuman animals, including but not limited to porcine insulin and porcine heart valves, are not considered xenotransplantation products.
- A xenotransplantation product recipient is a person who undergoes xenotransplantation.
- Intimate contacts of xenotransplantation product recipients include persons who have engaged in activities that could result in intimate exchange of body fluids including blood or saliva with a xenotransplantation product recipient. Examples of intimate contacts include, but are not limited to, sexual partners, household members who share razors or toothbrushes and health care workers or laboratory personnel with repeated percutaneous, mucosal or other direct exposures. Sharing of housing or casual contact, such as hugging or kissing without the exchange of saliva, would not be interpreted as intimate contact.
- Zoonoses are infectious diseases of animals that can be transmitted to humans through exposure to, or consumption of, animals infected with the disease.

III. BACKGROUND

With the success of clinical human allotransplantation, the demand for many human cells, tissues and organs in the treatment of human disease greatly exceeds the supply. Despite intensified efforts to enlarge the pool of human organ donors, there is a critical shortage of human organs available for transplant. Approximately half of patients with end-stage disease of vital organs - such as liver, heart, and kidney - die while awaiting transplantation. Meanwhile, scientific advances have begun to overcome the formidable immunologic barriers to the survival of animal transplants in humans. Examples of these advances include the development of potent new immunosuppressive drugs (Ref. 1), genetically engineered (transgenic) animals (Ref. 2), and new biomaterials for encapsulation (Refs. 3, 4).

The unmet and growing demand for human cells, tissues, and organs, coupled with recent advances in the science of immunology and molecular biology mentioned above increased interest in the experimental use of live nonhuman animal cells, tissues, and organs to treat a wide variety of human diseases (Ref. 5). In the past, xenotransplantation products have been obtained from a variety of animal species including rabbits, cows, pigs, chimpanzees, baboons, goats, and sheep. Recent xenotransplantation clinical trials focused primarily on porcine xenotransplantation products but have also included xenotransplantation products obtained from other non-human animals. Clinical trials have been proposed to assess the

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safety and effectiveness of xenotransplantation products in the treatment of a wide variety of human diseases ranging from severe life-threatening illnesses such as acute liver failure, to chronic diseases such as diabetes mellitus. Examples include the use of fetal pig brain cells to treat severe **neurologic** disease such as refractory Parkinson's Disease or Huntington's Disease (Refs. 6, 7). Pigs have been genetically engineered to make proteins that act as inhibitors of the human immune system to facilitate survival of a porcine xenotransplantation product in the human transplant recipient (Ref. 8). Ex vivo hemoperfusion through livers obtained from these transgenic pigs has been studied as a temporizing measure, or a bridge to treat fulminant liver failure until a human liver becomes available for transplant. Porcine hepatocytes encapsulated in an ex vivo hemoperfusion device have also been used in this manner.

Encapsulated pig pancreatic islet cells are proposed for the treatment of insulin-dependent diabetes mellitus (Refs. 9, 10). If successful, these clinical trials could provide another future therapeutic option for millions of insulin-dependent diabetic patients by diminishing or eliminating their need for insulin injections. At present, xenotransplantation remains highly experimental (Ref. 11).

The public has become increasingly concerned in the last few years about the potential infectious disease and public health risks associated with xenotransplantation. Because transplantation necessitates disruption of the recipient's usual protective physical and immunologic barriers, xenotransplantation may facilitate transmission of infectious agents to humans. Many of these agents may be currently unknown. These can include unknown retroviruses, which may remain latent for a long period of time before causing clinically recognized disease. Because they are integrated into the species genome, endogenous retroviruses may not be eliminated from source animals by herd health surveillance and screening programs. In the natural host, these endogenous retroviruses may not be expressed, but they may be able to productively infect cells of another species (xenotropic). The clinical consequences of the introduction of endogenous retroviruses into immunocompromised human hosts remain, in most instances, undefined (Refs. 12, 13, 14, 15, 16).

Xenotransplantation provides a unique environment for adaptation and cross-species transmission of infectious agents because: (a) the recipient is typically immune-suppressed; (b) in many instances, the xenotransplantation product is in direct contact with recipient's cells; and (c) if the xenotransplantation product is long-lived in the recipient, the chronic exposure of the recipient to virus may provide an environment facilitating adaptation of a virus to a human host. In particular, porcine endogenous retroviruses (PERV) have been shown to be transmissible to human cells in tissue culture (Refs. 17, 18, 19). Furthermore, simian foamy viruses have been able to infect human populations (Ref. 20). Therefore, the Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation, January 29, 2001 (Ref. 21) recommends that as an interim precautionary measure,

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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 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 (Section 2.5.11). Section 2.5.3 of the guideline discusses the potential risk for transmission of xenogeneic infectious agents to the recipient's family or contacts, especially sexual contacts. Section 4.2.3 also discusses the potential risk to certain health care workers.

On December 17, 1997, the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee recommended at an open public meeting that close contacts of xenotransplantation product recipients, as well as the recipients themselves, should not donate blood components or tissue, because these individuals are theoretically at risk of acquiring zoonoses, and of transmitting them through blood and tissue donation. FDA's Blood Products Advisory Committee discussed donor deferral issues related to xenotransplantation at an open public meeting on March 19, 1998. After further internal discussion, FDA concluded that since both in vivo exposure and ex vivo exposure to xenotransplantation products present avenues for acquiring zoonoses, donor deferral and product withdrawal policies should apply to both. However, FDA recognized that, on a case-by-case basis, deferral and withdrawal may not be warranted for certain ex vivo exposures, (such as exposure to a well-characterized cell line, or exposure across a physical barrier). FDA has also given consideration to the theoretical risk from exposure to cells, tissues or organs of nonhuman primates (Refs. 22, 23, 24). It was recently reported that baboon Cytomegalovirus (BCMV) could be detected in stored blood and duodenal samples obtained from a recipient of a baboon liver in a xenotransplantation procedure performed several years earlier (Ref. 25). In response to public concern particularly regarding the use of transplantation products from nonhuman primates, FDA issued the "Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans," in April 1999 (Ref. 26). This document states that, at the current time, FDA believes that there is not sufficient information to assess the risks posed by nonhuman primate xenotransplantation, and that clinical protocols proposing its use should not be submitted to the agency until sufficient scientific information exists addressing the risks. On December 30, 1999, FDA released for comment a draft guidance document entitled "Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Contacts" (Ref. 27).

On January 13, 2000, the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee, in an open public meeting, recommended to

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defer xenotransplantation product recipients from donating Whole Blood and blood components (16 to 0) and to allow case-by-case exceptions from deferral for certain ex vivo exposures (16 to 0). The committee also recommended to defer intimate contacts of xenotransplantation product recipients (9 to 7). The committee further recommended that Whole Blood, blood components, and pooled plasma (and its derivatives) containing material from a xenotransplantation product recipient be withdrawn from circulation (16 to 0), but that pooled plasma (and its derivatives) containing material from an intimate contact of a xenotransplantation product recipient should not be withdrawn from circulation (4 in favor of withdrawal, 9 against, 3 abstentions). The committee declined to recommend different withdrawal or deferral policies for exposure to material from non-human primates.

At a March 17, 2000, meeting of the Blood Products Advisory Committee, the committee recommended (5 to 4, with 3 abstentions) that the blood donor questionnaire be carefully modified to appropriately capture xenotransplantation product recipients and their intimate contacts without increasing the complexity of the questionnaire or detracting from known risk behaviors.

IV. RECOMMENDATIONS

A. Donor Deferral

1. You should defer indefinitely xenotransplantation product recipients from donating Whole Blood and blood components, including Source Plasma, and Source Leukocytes.
2. You should defer indefinitely Intimate contacts of xenotransplantation product recipients from donating Whole Blood, blood components, including Source Plasma, and Source Leukocytes. Intimate contacts are persons who have engaged in activities that could result in intimate exchange of body fluids, including blood or saliva, with a xenotransplantation product recipient. Examples of intimate contacts include:
 - a. sexual partners
 - b. household members who share razors or toothbrushes
 - c. individuals who have had repeated exposure to blood and body fluids through percutaneous inoculation (such as accidental needlestick) or through contact with an open wound, non-intact skin, or mucous membranes.
3. You should ask potential donors the following two questions, the first of which is a minor modification of a currently asked question on transplantation, and the second of which is a nested question set:

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- a. In the past 12 months, have you received blood, an organ, skin graft, or other tissue transplant from a human donor?
If the answer is yes, the potential donor should be deferred.
- b. Have you, any sexual partner, or any member of your household ever had a transplant or other medical procedure that involved being exposed to organs, tissues, or living cells from an animal?
If the answer is no, you should not defer potential donor on the basis of xenotransplantation exposure. If the answer is yes, then you should ask the potential donor the following question:

Was it you, a sexual partner or some other member of your household who had a transplant or otherwise was exposed to organs, tissues, or cells from an animal?

If the answer is “you” (the donor), defer. If the answer is “sexual partner”, defer. If the answer is “other member of your household”, you should ask the potential donor the following question:

Have you been repeatedly exposed to blood, saliva, or other body fluids from these individuals through deep kissing, shared toothbrushes, razors, needles, open wounds, or sores?

If the answer is “yes”, you should defer the potential donor.

4. FDA will consider on a case-by-case basis, deferral for certain ex vivo exposures, such as exposure to a well-characterized cell line, or exposure across a physical barrier.

B. Blood Product Quarantines and Withdrawals

1. You should withdraw Whole Blood and blood components (including unpooled plasma and Source Leukocytes) intended for transfusion or for further manufacturing into injectable products from distribution and hold in quarantine or destroy, if made from donations obtained from persons described in Section IV.A.1. or 2. You should consult with FDA on a case-by-case basis to determine deferral for certain ex vivo exposures, such as exposure to a well-characterized cell line, or exposure across a physical barrier.
2. You should withdraw from distribution and quarantine in-date plasma derivatives (including pooled plasma) that were made from plasma containing a donation obtained from xenotransplantation product recipients. You should consult with

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FDA on a case-by-case basis regarding withdrawal and quarantine for certain ex vivo exposures, such as exposure to a well-characterized cell line, or exposure across a physical barrier. You should not withdraw and quarantine in-date plasma derivatives (including pooled plasma) made from plasma containing a donation from an intimate contact of a xenotransplantation product recipient.

3. You should label quarantined products described in Sections IV.B.1. and B.2. above, for further manufacturing into non-injectable products or for research use with recommended labeling described below in Section V.

V. LABELING OF PRODUCTS DISTRIBUTED FOR RESEARCH OR INTENDED FOR FURTHER MANUFACTURING INTO NON-INJECTABLE PRODUCTS

As appropriate, you should label products intended for use in research or for further manufacturing into non-injectable products with the following statements:

1. “Biohazard;”
2. “Collected from a donor determined to be at risk for a zoonosis;” and
3. “For laboratory research use only” or “Intended only for further manufacturing into non-injectable products.”

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