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

DRAFT GUIDANCE

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DRAFT- Not for Implementation

Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance document is to inform all registered blood and plasma establishments, and establishments engaged in manufacturing plasma derivatives of the Food and Drug Administration's (FDA) recommendations concerning the indefinite deferral from blood donation of xenotransplantation product recipients and their contacts. 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 in close contact with a xenotransplantation product recipient.

II. BACKGROUND

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. Xenotransplantation products include live cells, tissues or organs used in xenotransplantation. A xenotransplantation product recipient is a person who receives or who undergoes ex vivo exposure to a xenotransplantation product. Close contacts of a xenotransplantation product recipient are defined as household members and others with whom the recipient participates in activities that could result in exchanges of bodily fluids. 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.

With the success of clinical human allotransplantation, the demand for many human cells, tissues

[1]This guidance document represents the agency current thinking with regard to possible risk of transmission of zoonoses by xenotransplantation product recipients and their contacts, through blood and blood products. It does not create or confer any rights, privileges, or benefits on or for any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

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 (1), genetically engineered (transgenic) animals (2), and new biomaterials for encapsulation (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 (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 cows. Clinical trials have been proposed to assess the 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 (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 (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 (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 (11), and current clinical trials in xenotransplantation are first and foremost clinical safety studies.

Concerns have arisen in the last few years about the potential infectious disease and public health risks associated with xenotransplantation. Zoonoses are infectious diseases of animals that can be transmitted to humans through exposure to, or consumption of, animals. Because transplantation necessitates disruption of the recipient's usual protective physical and immunologic barriers, xenotransplantation may facilitate transmission of known or as yet unrecognized agents to humans. These can include unknown retroviruses, which may remain latent for a 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 consequence of the introduction of endogenous retroviruses into immunocompromised human hosts remains, in most instances, undefined (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 primed for 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 (17, 18, 19). Furthermore, simian foamy viruses have been able to infect human populations (20). Therefore, the Draft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation, of September 23, 1996 (21), indicated that patient consent forms should state clearly that xenotransplantation product recipients should never, subsequent to receiving the transplant, donate Whole Blood, blood components, Source Plasma, Source Leukocytes, tissues, breast milk, ova, sperm, or any other body parts for use in humans (Section 2.5.9, page 49923). These draft guidelines also include outlines of health surveillance programs and principles for screening candidate source animals for infectious agents of concern. Section 2.5.3 of the guideline discusses the potential risk for transmission of xenogeneic infectious agents to the recipient's family or close contacts, especially sexual contacts. Section 4.3.3 of the guideline also discusses the potential risk to certain health care workers.

On December 17, 1997, the recently established 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 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 xenotranplantation 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 in vivo and ex vivo exposures. 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). Furthermore, the greatest theoretical risk probably is from exposure to cells, tissues or organs of nonhuman primates (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 (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 (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.

In the case of plasma derivatives, current manufacturing methods are likely to mitigate many of the potential infectious risks, particularly for enveloped agents such as retroviruses. In addition, there are usually serious supply implications to withdrawing plasma derivatives. Therefore, withdrawal of plasma derivatives generally is not recommended for donor exposures to animal sources other than nonhuman primates.

This guidance document contains FDA recommendations to blood establishments regarding donor deferral and product disposition.

III. RECOMMENDATIONS

A. Donor Deferral

1. Persons who have received xenotransplantation products should be indefinitely deferred from donating Whole Blood and blood components, including Source Plasma, and Source Leukocytes.

2. Persons who are close contacts of xenotransplantation product recipients should be indefinitely deferred from donating Whole Blood, blood components, including Source Plasma, and Source Leukocytes.

3. Health care workers, including laboratory personnel, and other individuals who have had contact with blood and body fluids from a xenotransplantation product recipient, through percutaneous inoculation (such as accidental needlestick) or through contact with an open wound, non-intact skin, or mucous membranes should be indefinitely deferred from donating Whole Blood and blood components, including Source Plasma, and Source Leukocytes.

4. Potential donors should be asked the following three questions:

    a. Have you, your sexual partner, any member of your household, or any other close contact ever received a transplant of living cells, tissues or organs from

any animal source?

b. Have you, your sexual partner, any member of your household, or any other close contact ever received human body fluids, cells, tissues or organs that came into contact outside of the body with live cells, tissues or organs from an animal?

c. Have you ever come into contact with blood or body fluids from a xenotransplantation product recipient through injury, accidental needlestick, an open wound, non-intact skin, or mucous membranes?

5. Potential donors answering questions 4.a., b., or c., affirmatively should be indefinitely deferred unless the nature of the exposure to the contact is unlikely to result in the exchange of bodily fluids and the medical director concurs that deferral is not warranted.

6. Deferral for certain ex vivo exposures, such as exposure to a well-characterized cell line, or exposure across a physical barrier, may not be warranted and will be considered by FDA on a case-by-case basis.

B. Blood Product Quarantines and Withdrawals

1. Whole Blood and blood components (including unpooled plasma and Source Leukocytes) intended for transfusion or for further manufacturing into injectable products, if made from donations obtained from persons described in Section III.A.1., 2., or 3., should be withdrawn from distribution and held in quarantine or destroyed. Exceptions for certain ex vivo exposures, such as exposure to a well-characterized cell line, or exposure across a physical barrier, may be considered by FDA on a case-by-case basis.

2. In-date plasma derivatives (including pooled plasma*)* that were made from plasma containing a donation obtained from persons described in Sections III. A.1., 2., or 3., should be withdrawn from distribution and quarantined or destroyed only if the xenotransplantation product is from, or has been exposed to nonhuman primate cells, tissues or organs. Withdrawal and quarantine may not be warranted for certain ex vivo exposures, such as exposure to a well-characterized cell line, or exposure across a physical barrier, and will be considered by FDA on a case-by-case basis. Withdrawal is not recommended for donor exposures to animal sources other than nonhuman primates.

3. Quarantined products described in Sections III.B.1. and B.2. above, that are distributed for further manufacturing into non-injectable products or for research use should be labeled consistent with recommended labeling described below in Section IV.

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

Products intended for use in research or for further manufacturing into non-injectable products should be appropriately labeled 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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