AMERICAN
ASSOCIATION
OF BLOOD BANKS

1693 '00 FEB 29 P1:31

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket #99D-5347: 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.

To Whom It May Concern:

The American Association of Blood Banks (AABB) is the professional association for approximately 2200 institutions engaged in the collection and transfusion of blood and blood products, including all American Red Cross blood services regions, independent community blood centers, hospital-based blood banks and transfusion services, and more than 8500 individuals engaged in all aspects of blood collection, processing and transfusion. Our members are responsible for virtually all of the blood collected and more than eighty percent of the blood transfused in this country. The AABB's highest priority is to maintain and enhance the safety of the nation's blood supply.

The AABB is pleased to provide written comment on the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research's (CBER) draft guidance setting out precautionary measures to reduce the possible risk of transmission of zoonoses by blood and blood products from xenotransplantation recipients and their contacts.

Background

Xenotransplantation is an exciting emerging technology that holds future promise for ameliorating the shortage of donor tissues for the treatment of serious, disabling diseases.

Recognizing the important potential risk of transmitting zoonotic pathogens to patients by this route, we agree that xenotransplant recipients are unacceptable donors of allogeneic blood and tissue. Parenthetically, because of donor restrictions regarding medication use and general health, virtually no xenotransplant recipient would be a qualified blood donor at this time.

This theoretical risk was well articulated in August 1996 in the *Draft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation* which states "Consent forms should state clearly that xenograft recipients should never, subsequent to receiving the transplant, donate Whole Blood, blood components, Source Plasma, Source Leukocytes, tissues, breast milk, ova, sperm, or any other body parts for in humans." The language appropriately recognizes the primary responsibility of the transplant community for the apprisal of their patients about zoonotic risks.

8101 Glenbrook Road ♦ Bethesda, MD 20814-2749 ♦ Phone: (301) 907-6977 ♦ Fax: (301) 907-6895
Web site: www.aabb.org ♦ Email: aabb@aabb.org

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We believe strongly that this aspect of the HHS guidance should be implemented. Even pending formal implementation of such guidance, FDA can insist on inclusion of such information in consent procedures as a condition for acceptance of clinical protocols for xenotransplantation.

Blood collection facilities can reinforce the prohibition on donation by including the xenotransplant exclusion in the written materials blood donors are required to study before each donation. This avoids addition of time consuming, confusing and unvalidated questions FDA suggests adding to the donor interview in this guidance.

Specific Concerns

That said, several aspects of the draft guidance are problematic.

Donor screening is already lengthy and complex. The AABB Uniform Donor History (sanctioned by FDA) contains 32 separate elements including inquiries into highly sensitive personal areas of sexual activity and drug use and references to such rare diseases as babesiosis and the transmissible spongiform encephalopathies. FDA proposes to add three complex questions to this process. REDS investigators (Williams et al, JAMA 277:967-972, 1997) have reported that 1.8% of anonymously surveyed accepted blood donors admit to deferrable risks, and we suspect that a substantial proportion of that is due to the length and complexity of the donor interview.

A related concern is that increasing the complexity of the donor screening process for marginal theoretical risks may detract from its efficacy for documented risks like traditional viral transfusion associated infections and malaria. The result is a paradoxical decrement in transfusion safety.

In fact, at its January 13, 2000 meeting, the Xenotransplant Subcommittee of the Biological Response Modifiers Advisory Committee endorsed our position that primary responsibility for notification and education of xenotransplant recipients about refraining from blood and tissue donation lies with the institution performing the clinical trial.

We maintain that proposed donor questions in this draft are too arcane to add to the current screening process and will produce donor confusion. This will result in unneeded deferrals at a time of borderline blood supply adequacy and declining donations. At a minimum, additional questions proposed by FDA for the reduction of *de minimis* risk must be validated for sensitivity, specificity and positive predictive value before being added to what is already referred to as the "donor interrogation" process.

The requirement to defer as blood donors "sexual partner(s), any member of your household, or any other close contact" for deferral is ambiguous (lacking concise definition of household and other close contact). More important, this requirement for deferral is unsupported by any evidence of transmission of potential or unrecognized pathogens to such contacts after xenotransplantation. Deferral of "health care workers, 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" is subject to the same criticism.

It is a slippery slope from such donor deferrals to disqualification of large populations with significant occupational animal exposures such as abattoir workers, farmers, veterinarians, and medical researchers working with large animal models.

We suggest that a risk assessment be undertaken among those with close contact to the relevant species for evidence of transfusable disease associations that would support zoonotic transmission of disease causing organisms. Given the small numbers of xenotransplants currently

being performed and the potentially large populations with contact to nonhuman primates and swine, these epidemiological studies can be carried out long before xenotransplantation becomes prevalent, constituting a zoonotic threat to significant numbers of patients and their contacts.

Summary

- We accept the necessity to defer recipients of xenotransplants. We respectfully suggest that the transplant programs have primary responsibility to initiate this process as part of informed consent.
- Blood collection facilities can reinforce this with written information.
- We suggest that the addition of unvalidated donor interrogation questions for the theoretical risks of xenotransplantation (or any theoretically transmissible entity) may, at worst, paradoxically increase other risks of transfusion, and at best will contract further an already shrinking donor base. At a minimum such proposed questions must be validated for a minimum level of sensitivity, specificity and predictive value as would any *in vitro* diagnostic assay required by FDA.
- Deferral for contact with xenotransplant recipients is unwarranted at present and the risk of such contact is amenable to study in populations with occupational exposure to the relevant species.

Thank you again for this opportunity to comment.

Sincerely,

Paul M. Ness, MD
President

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8101 Glenbrook Road • Bethesda, Maryland 20814-2749

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FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE, ROOM 1061
ROCKVILLE, MD 20852