America's Blood Centers

OUR MEMBERS SERVE COMMUNITIES NATIONWIDE

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May 8, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.

Re: Docket No. 00D-1662: Draft *Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans.*

Dear Docket Officer:

America's Blood Centers (ABC) is pleased to have the opportunity to submit comments on the Center for Biologics Evaluation and Research's draft guidance on the production, testing, and evaluation of products intended for use in xenotransplantation. For your information, ABC represents nonprofit blood centers that collect approximately half of the volunteer blood and blood components for transfusion in the United States.

Our comments address Section J (Informed Consent) of the draft guidance, which states: *"As an interim precautionary measure, xenotransplantation product recipients and certain of their contacts should be deferred indefinitely from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."*

Xenotransplant Recipients Should be Deferred from Donating Blood or Plasma. ABC members agree with CBER that blood donated by xenotransplant recipients may pose a theoretical risk to transfusion recipients because of the potential for transmission of known or as-yet unknown infectious agents. We are concerned by experiments documenting the transmission of porcine endogenous retroviruses (PERV) to human cells in *in vitro* tissue culture. Thus, ABC agrees that xenotransplant recipients should be deferred from donating blood or tissues.

Xenotransplant Contacts. Section J2 (a)(i) states that "*the patient should consent to inform his current and future contacts of their potential risks from the source animal species and of their deferral from blood donation.*" The section states further: *"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*

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of deliberations between FDA and its advisors. . . . Additionally, the range of contacts who should be deferred from blood donation will be clarified after further public discussion."

ABC is concerned that although the suggested definition of contacts has been narrowed since previous CBER guidance on xenotransplantation, it still casts too broad a net and could defer many perfectly safe blood donors—especially since the risk to contacts of xenotransplant recipients still has not been accurately assessed. For example, the terms "repeated [exposure]" and "direct exposure" are not defined in the draft guidance. It is important to note that a major factor in the transmission of zoonotic pathogens to xenotransplant recipients is that the immunosuppression required to prevent rejection will render them uniquely susceptible to infection. In contrast, immunosuppression is not an issue in contacts. We are encouraged that CBER plans continue to consult with its advisors on the issue of contacts at risk.

ABC Strongly Opposes Adding Specific Donor History Questions on Xenotransplantation

- **ABC urges CBER to state in the final guidance that adding specific questions about xenotransplantation to the blood donor medical history is unwarranted for achieving blood safety.**

- **To ensure that the small number of people who already have received xenotransplants as defined in the draft guidance not donate blood in the future, CBER should require that individuals at theoretical risk for a zoonotic pathogen secondary to xenotransplantation be notified retrospectively by their transplant centers that they are indefinitely deferred from donating blood or tissues.**

ABC members believe that the responsibility for the safety of xenotransplants should be the responsibility of the people and institutions performing these experiments. Recipients of xenotransplants are known to the institutions and programs that sponsored the transplant. Because of the close contact these institutions have with clinical trial participants, they have the specific means to notify individuals at risk and require that they abstain from donating blood and tissues. This certainly will be more effective than searching for the rare individual at theoretical risk among the millions of individuals who volunteer to donate blood.

Moreover, in addition to blood and plasma, xenotransplant recipients and their contacts potentially could donate organs, tissue, breast milk, ova, sperm, and other body parts. Too many types of organizations are involved at the donor end of the process to place the responsibility there. For example, in many states, organ donors are solicited through driver's license bureaus. If the responsibility for notifying and counseling xenotransplant recipients about donation is removed from the clinical trial site, who would bear the responsibility for ensuring that a xenotransplant patient or close contact did not unknowingly sign up for this program? This information would likely not be readily available in an emergency—especially for a "close contact." We do not believe that it would be prudent to require blood centers to shoulder the responsibility for blood donation, yet allow the other types of donations to occur with less attention to this safety issue.

We would like to point out that at its January 13, 2000 meeting, CBER's Biological Response Modifiers Advisory Committee's Xenotransplantation Subcommittee voted that given the very small number of xenotransplant recipients to date and the fact that they are enrolled in closely-monitored clinical trials, adding specific questions to the blood donor medical history about a history of xenotransplantation or

close contact with xenotransplant recipient is unnecessary. Instead, the panel recommended that education about not donating blood or plasma should be provided by the institutions performing the trials.

At its March 24, 2000 meeting, CBER's Blood Products Advisory Committee also voted against adding specific donor questions on xenotransplantation, saying that this was the role of the transplant team. The committee also voted against requiring blood collection facilities to provide educational materials to about xenotransplantation to blood donors

ABC agrees with the conclusions of both of these expert panels that adding questions to the medical history about xenotransplantation or contact with a xenotransplant recipient is inappropriate and actually may increase the risk of transmission of known infectious diseases to blood recipients. Given the complexity of the medical history form, any additional questions risk diverting the attention of donors from those related to major risks to the blood supply (*i.e.*, donors in the window of seroconversion for hepatitis and HIV).

Consider the following regarding the blood donor medical history:

- Additional history questions affect a large number of donors.
- Volunteer blood donors donate over 13,000,000 units of whole blood and apheresis platelets every year; the plasma industry collects double this number of units of plasma by plasmapheresis every year.
- Volunteer donors of whole blood and donors of source plasma are subjected to questions required by CBER and the American Association of Blood Banks (AABB) every time they donate.
- The current medical history questionnaires are extensive.
- The AABB Uniform Donor Questionnaire (*Association Bulletin* #99-10, December 2, 1999) has 32 separate questions.
- Many of these questions are complex and refer donors to unusual entities and issues, including Babesiosis, Chagas, Creutzfeldt-Jakob Disease, bovine derived insulin, human-derived pituitary growth hormone, Acitretin, Proscar, dura mater, Isle of Man, Channel Islands, Immunoglobulin, and clotting factor concentrates.
- Other history questions address risk behavior, but focus donors' attention on events that took place a long time ago, despite evidence that the major risks of transmission of infectious disease are associated with window periods of weeks, *e.g.*, "Have you had sex with another men since 1977?"

Additional Donor Questions Must be Validated Before Implementation. On a more general issue, ABC members are extremely concerned about the lack of information about the sensitivity, specificity and predictive value of donor questions. There have been no studies showing the impact of additional complex questions on the safety (sensitivity) or availability (specificity) of the blood supply. Moreover, there is no quantitative assessment of the benefit of such additional questions (positive predictive value).

ABC believes that before mandating any new additions to the donor medical history, CBER must require scientific documentation that the new questions will not decrease the safety of the blood supply for known infectious agents such as HIV, HCV and HBV.

Thank you for the opportunity to comment. I would be glad to answer any question you may have.

Yours truly,

Celso Bianco (jz)

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