

American Red Cross

National Headquarters

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March 24, 2000

Kathryn C. Zoon, Ph.D.
Director
Center for Biologics Evaluation and Research
Food and Drug Administration (HFM-1)
Suite 200 North
1401 Rockville Pike
Rockville, MD 20852-1448

RE: 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 - [Docket No. 99D-5347, 64 Fed. Reg. 73562 (Dec. 30, 1999)]

Dear Dr. Zoon:

The American Red Cross (ARC/Red Cross) wishes to thank the Food and Drug Administration (FDA) for the opportunity to comment on the draft guidance regarding *Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products From Xenotransplantation Product Recipients and Their Contacts*.

ARC is the largest supplier of blood products and one of the largest providers of blood services in the United States. Each year, the Red Cross collects, processes, and distributes approximately six million units of whole blood, representing half the nation's blood supply. The blood donated by Red Cross volunteers is also recovered and processed or fractionated into plasma derivatives. After collection and recovery, these plasma units are transported to several vendors with whom we have established contracts to manufacture antihemophilic factor, intravenous immune globulin, albumin and solvent-detergent treated products under the FDA licenses of those companies. These plasma products are distributed under the American Red Cross label to hospitals, hemophilia treatment centers, and other providers.

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ARC will be subject to the guidance as it applies to both the collection of blood and to product quarantine and withdrawal recommendations. Thus, we have outlined our views on the draft guidance below.

I. Summary of ARC's Views

On January 13, 2000 ARC and several other organizations involved in the collection, processing or use of blood and plasma derivative products testified before the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee (Subcommittee) with regard to the proposed draft guidance. ARC would first like to restate its views on the draft guidance as articulated at that meeting:

- ARC believes that a deferral policy for Xenotransplantation patients is appropriate.
- The only donors who need to be deferred are those receiving the transplant itself.
- Additional donor questions are unnecessary.
- The terms used to define which types of transplantations and/or exposure are so rarely used and unfamiliar to the public that they would require substantial revision and/or clarification before the guidance could be implemented.
- The majority of the public is not familiar with Xenotransplantation, thus there is likely to be confusion and lack of intended effect, since almost all of the potential donors who may think they are affected will not have been.

II. Donor Questions (Draft Guidance - Section III.A.4.)

ARC is particularly concerned with the addition of three new questions to an already overly burdensome donor questionnaire. While well intended, Red Cross believes that reliable implementation of these questions would be difficult, if not impossible, due to their lack of clarity. Many donors already regard the numerous existing questions on ARC's blood donor questionnaire as overly intrusive. Donors may regard the inclusion of these questions as adding a delay in the donation process, rather than as contribution to public health or safety.

The terms "close contact" used in question 4.a. and 4.b. and the term "contact" used in question 4.c. are illustrative of this concern. For example:

- The lack of definition of "close contact" and "contact" will lead to varying interpretations and therefore inconsistent application of the questions.
- Without a clear definition, donors may require extensive clarification while preparing to donate at the blood collection center, requiring additional time to complete the donor screening process. The recommendations of the subcommittee were to include only intimate contacts of Xenotransplant recipients. This term is more easily definable, and perhaps more appropriate.
- Even if better definitions exist, it is likely that many donors will not know whether the contact is a Xenotransplant recipient or not.

At the Subcommittee meeting, there was a vote to change the term "close contact" to "intimate contact". Red Cross agrees that this is an improvement, in that "intimate contact" more directly addresses exposures of potential concern, and it could be defined with greater clarity. We hope that the duty to inform Xenotransplant recipients and "intimate contacts" will rest with the informed consent process at the transplant center as suggested by the Subcommittee. More importantly, ARC agrees with the concerns expressed at the Subcommittee meeting that there is a greater risk to public health by the potential for compromising the availability of the blood supply. Adding further time to the already lengthy donation process may discourage donors who already object to the process' length. They may choose to donate less frequently or avoid donation all together.

III. Alternative Approaches

As ARC and others mentioned during the Subcommittee meeting, we believe that there are alternative, and potentially far more effective, methods to help mitigate the risk of potential transmission of disease through Xenotransplantation. Specifically, at the time of the transplantation, the investigators conducting the transplantation could counsel recipients and their families regarding their blood donation options.

The investigators will have conducted extensive health assessments and health history evaluations of these patients, and may even interact with their families. Thus, their direct patient interaction, and the investigator's greater familiarity with Xenotransplantation's overall risks, renders this approach a far more effective way to minimize the risks of disease transmission.

We believe such steps, separate from the donation process, will far more efficiently reach the very few Xenotransplantation recipients and their families, estimated at no more than about 50 per year, than attempting to screen the 12,000,000 or more blood donors each year.

IV. Blood Product Quarantines and Withdrawals (Draft Guidance - Section III.B)

Our concerns for the blood product Quarantine and Withdrawal policies described in Sections III.B.1, III.B.2 and III.B.3 parallel our concerns about the donor deferral policies. Specifically, additional withdrawal policies will require notification to consignees, which will unnecessarily worry recipients of products from such donors and raise questions about the theoretical risk and harm to recipients. The blood industry will be at a loss to provide such guidance. In addition, when the risks of disease transmission are theoretical at best, there is a serious consideration that the policies may do more harm than good by reducing the availability of the blood supply. Even if the concern for the supply was lessened, existing manufacturing methods, and efficient viral inactivation procedures are likely to eliminate many of the potential infectious risks, especially for plasma derivative products.

Red Cross encourages FDA to reevaluate these withdrawal policies, and consider rescinding them for all circumstances, except where it is found that the donor him/herself is a Xenotransplantation recipient.

V. Providing Electronic Information on Xenotransplantation Recipients to Blood Collection Centers

During the Subcommittee meeting, it was suggested that FDA provide blood centers with a computerized list of Xenotransplantation recipients. The idea that as donors enter the collection site, they could be checked against the list to ensure they are not Xenotransplantation recipient. On the blood center side, we have the technological capacity and privacy protection processes in place to keep the list confidential if the FDA and Xenotransplant recipients choose this path. However, there are other considerations.

One is the additional time and extensive procedures for name verification that would be added to the donation process to work with such lists. Moreover, having the list will likely result in more unnecessary deferrals should any question regarding the accuracy of name matching occur.

More importantly, is the concern for confidentiality of the Xenotransplant recipient's medical records. At a minimum, permission will be needed from Xenotransplantation recipients for including their names on computerized lists that would then be distributed to blood centers nationally.

VI. Revisions Proposed to BPAC March 17, 2000

During the Blood Products Advisory Committee (BPAC) meeting on March 17, FDA summarized the discussion and vote at the Xenotransplantation Subcommittee meeting. FDA also presented several revisions to the Guidance, including a revision to the previous questions and suggested language to be added to donor educational materials. ARC has reviewed these materials and believes that the revisions as proposed do not fully address the concerns we have expressed above and in our testimony on January 13 about the Draft Guidance. (see Attachment)

In particular, ARC does not believe that additional questions are necessary, and the revisions do not alleviate several additional comments describe by the ARC and others. Specifically, the additional questions will slow the donation process. Further, without validation, there is no assurance the revised version will generate accurate responses.

ARC continues to urge FDA to consider the alternative of discussing implications for blood donation with Xenotransplantation recipients and their relatives at the time of transplant.

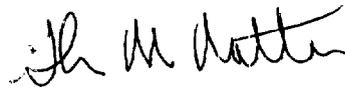
VII. Revision of the Draft Guidance

Based on the information discussed at both the Subcommittee meeting and the BPAC meeting, as well as public comment likely to be received on this topic, it is likely that FDA will revise the draft guidance prior to finalization. We believe that the Agency has, so far, very responsibly managed this issue, both by accessing the appropriate advisory Committees and by soliciting public comments. In particular, we appreciate the opportunity to file written comments with FDA after the BPAC meeting so that an assessment of the additional work performed after the Subcommittee meeting might be possible.

However, we anticipate considerable changes as a result of the Committee meetings and the public comments submitted to date. Therefore, we wish to be able to continue our participation as the Agency's policies unfold in this area. ARC requests that FDA reissue the guidance as a revised draft, prior to issuing a final version, so that the public may file comments on what is likely to be a substantially different guidance.

If there are any questions regarding this letter, please contact Anita Ducca, Director, Regulatory Relations at 703-312-5601.

Sincerely,



Glenn M. Mattei, Esq.
Senior Director, Quality Assurance
and Regulatory Affairs
Biomedical Services
American Red Cross

Attachment

**TESTIMONY BY
Rebecca Haley, MD**

**ON BEHALF OF
THE AMERICAN RED CROSS**

On FDA's Draft "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"

Docket No. 99D-5347

January 13, 2000

The American Red Cross is pleased to have the invitation to speak regarding the FDA's recommendations for the prevention of transmission of zoonotic pathogens from xenotransplantation recipients through blood transfusions. The American Red Cross collects over six million units of blood from volunteers each year in the United States. I am Rebecca Haley, Senior Medical Officer at Biomedical Headquarters responsible for the medical aspects of donor qualification.

ARC agrees that a deferral policy for Xenotransplantation is appropriate. We understand there is a theoretical risk of disease transmission from recipients of xenotransplants if they should become blood donors in the post-transplant period. Facilities performing xenotransplants are guided by Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation (1996) to include in their consent form for patients that they should no longer be blood donors. The current proposed donor questions assume that this guidance has not been followed. In addition, we are very concerned that the guidance, in its current form, needs considerable clarification and revision before it would be workable for the blood collection facilities. The guidance is quite expansive and includes a number of groups in the deferred donor category.

ARC believes that the only donors who need to be deferred are those receiving the transplantation itself. We do not believe there is justification for deferral of other donors such as those in the same household, or in "close contact" with Xenotransplantation recipients. The recipient is iatrogenically immunocompromised as an element of the treatment necessary for the patient to tolerate the graft. This treatment puts the recipient at risk for such infections. To date there have been no reports of spread of zoonoses to "close contacts" or household members.

Additional donor questions are unnecessary. The donor questions as suggested would not elicit the expected results since the concepts about xenotransplantation are not well known by the general public. We currently have a question that asks the donor if he/she has received a blood transfusion, an organ or tissue transplantation. We could include information in the "What You Must Know" section to point out that organ xenotransplants are appropriate for reporting in this section. This question could easily

apply to Xenotransplantation tissue, as well. If the donor answers affirmatively, the Health Historian can ask additional questions, separate from the questionnaire, about their transplantation experience and whether it involves animal tissue.

The terms used to define which types of transplantations and/or exposures are vague. Better definitions are needed as well as more examples. Deferral policies are based on criteria discussed in the guidance, yet those criteria are either not defined or only vaguely defined. These include such concepts as Xenotransplantation of *living vs. non-living* cells. FDA appears to allow those receiving "nonliving cells" to donate, but those who receive living ones may not. The guidance gives a few examples, but not a clear definition. Without clear definitions, collection staff will not be able to assess donors that answer affirmatively to a yes response by a donor. Thus, deferral policies are not clear for those receiving organ or tissue transplants not included as one of the guidance examples. There is also a need for better definitions of *in vivo vs. ex vivo* exposure, particularly as it may apply to such potential blood donors as laboratory personnel. Similarly, this concern applies to animal workers, Veterinarians, veterinary staff, zoo workers, and others who may come in contact with animals alive or freshly killed such as farmers or meat slaughtering or packing staff. This could disqualify a very significant percentage of the donor population.

The majority of the public is not familiar with Xenotransplantation or disease transmission by this route. Thus, there is likely to be a significant amount of confusion at donor collection sites and a lack of consistency in implementation. The suggested questions talk about medical situations that are very unfamiliar to most Americans. If such a line of questioning is pursued and the potential donor does not know what you are talking about, can an "I don't know" suffice for a "No" answer? Section III.A.5. allows discretion on the part of the medical director to permit donation if "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." The medical director typically accepts or defers donors on evidence of risk. For well, non-immunocompromised contacts, there is no medical evidence for deferral. When we defer donors they expect a factual reason for the deferral. We already push the limit of tolerance of our donors with the current questions with very long and arbitrary time frames concerning deferral events. Now if we implement another set of "have you ever" questions with vague indication, it will test the patience of most and enrage other donors. These questions engender an adversarial tone in the donor interview that discourages donors from returning. As we discuss these matters most of the United States is on appeal for blood donors and elective surgeries are being cancelled. The potential for harm from a lack of blood donors is very real and has often been highlighted by the Secretary of Health and Human Services, Dr. David Satcher, as a serious concern for medicine in the United States.

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. Withdrawals of plasma derivatives have caused serious supply problems in the recent past. This would be likely to happen again with definite potential for harm where the theoretical exposure to zoonoses does not have a definable risk.