

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

Re: Docket No. 99D-5347

May 3, 2002

Draft Guidance for Industry - Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product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 Intimate Contacts (Deadline for comments, May 15, 2002).

Federal Register, February 11, 2002

To whom it may concern:

The Campaign for Responsible Transplantation (CRT) is an international coalition of physicians, scientists and 90 public interest groups representing millions of people concerned about the public health risks inherent in xenotransplantation.

On January 24, 2000, CRT submitted comments in response to the previous draft of this guideline. Concerns remain about the current draft.

In this draft guideline, the Food and Drug Administration (FDA) again acknowledges that *“xenotransplantation may facilitate transmission of infectious agents to humans . . . [many of which are] currently unknown. These can include unknown retroviruses which may remain latent for a long period of time before causing clinically recognized disease.”*

Despite such alarming statements, however, the current draft guideline - like its predecessor - ignores its own warnings.

The FDA proposes to use a blood donor questionnaire to screen out donations of whole blood and blood components from xenotransplant patients, their intimate contacts and household members, and healthcare personnel who may have been exposed to blood or fluid from a xenograft patient (i.e. via accidental needlestick.)

This assumes that the use of a questionnaire is the best way to prevent these individuals from donating blood; it assumes that patients will be honest and forthcoming about their sexual contacts and practices when asked; and it assumes that proper records will be kept at all times. With the safety of the nation's blood supply at stake, we contend that a questionnaire may not be an adequate enough tool to do the job at hand. Enlisting the help of patients' physicians to ensure that they do not donate blood, and launching public education campaigns in hospitals and blood centers could help.

In our previous submission to this docket, we suggested that a national computerized name-based registry, listing the names and addresses of xenograft recipients and their intimate contacts might allow the identification of these individuals, to prevent them from donating blood. To be sure, such a registry would be plagued by numerous legal problems related to privacy rights, would be expensive to set up and manage, and will always be vulnerable to human error (such as if patients marry, change their names, relocate without informing regulatory authorities, or if hospital procedures are not carried out correctly.) However, CRT sees it as the best hope we have of tracking potentially infectious individuals and preventing them from donating blood.

The FDA also proposes to decide, on a case-by-case basis, whether to consider blood donations from patients who have had certain ex vivo exposures to live animal cells, such as exposures to “well-characterized cell lines” (which have yet to be defined) or “exposures across a physical barrier” (presumably porcine hepatocytes encapsulated in an ex vivo hemoperfusion device, and/or encapsulated porcine islet cells).

This case-by-case decision-making is being proposed despite the FDA’s own acknowledgement in this guideline that “both in vivo exposure and ex vivo exposure to xenotransplantation products present avenues for acquiring zoonoses.”

Indeed, noted virologists and microbiologists have expressed concern about the public health risks inherent in *all* forms of xenotransplantation, including ex vivo exposures. In October 1997, virologist Jonathan Stoye stated that “if you’re going to hook someone up to a pig liver outside their body for a long period, I don’t think it’s much safer than an actual transplant.”¹

In its Registration Statement to the Securities and Exchange Commission (June 20, 1997), Circe Biomedical, Inc., maker of the HepatAssist ex vivo “xenoperfusion” device, “it is possible that” xenotransplantation products will “transmit viruses, infectious diseases or other contaminants from non-human species to human patients.”

According to Dr. John Coffin, a leading researcher on the issue, “some kind of infection” appears to be “virtually an inevitable consequence” of xenotransplantation.²

So although the FDA proposes to consider blood donations from patients who have had certain ex vivo exposures to live animal cells, such as “well-characterized cell lines,” we would like to point out that a “well-characterized” line of monkey kidney cells was used in the production of polio vaccine given to 30 million people between 1955 and 1963. It is now believed that the vaccine was tainted with Simian Virus 40, which has been linked to non-Hodgkin’s lymphoma.³

Genzyme has used 3T3 mouse cells to grow layers of human skin for burn treatments. Though at a January 13, 2000 meeting of the FDA’s Xenotransplantation Subcommittee, it was revealed that the

¹ Michael Day. Tainted Transplants. *New Scientist*, 18 October 1997.

² Xenotransplantation Subcommittee, Biologics Response Modifiers Advisory Committee, transcript, Dec. 17, 1997, p.35

³ Anon. Vaccine virus ‘cancer link. BBC News online, 8 March 2002.

company had not performed FDA-required tests to determine whether its mouse cells could infect human cells *in vitro*.⁴

These are some of the reasons why CRT is concerned about the term “well characterized cell line” and why we strongly recommend that FDA **not** allow blood donations from xenotransplant patients who have had ex vivo exposures to live animal cells.

In this guideline, the FDA has also made 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.*”

This clearly acknowledges that both the patient monitoring and blood collection systems are vulnerable to human error.

In our January 24, 2000 comments, we pointed out that the U.S. blood supply has historically been plagued by problems including weak donor screening, negligence by blood product manufacturers and blood facilities, insufficient communication to patients about disease risks, vulnerabilities and gaps in current administrative procedures, decision-making compromised by personal biases, weak regulatory oversight by FDA, and contamination by viruses like HIV and hepatitis.

Indeed, on March 27, 2002 CBER announced the recall of Bayer Corporation’s Koate-DV1 Antihemophilic Factor (Human) after learning that a plasma unit used to manufacture the product had elevated levels of parvovirus B19, creating a “theoretical risk for transmission.”⁵

Infection with Parvovirus B19 can cause viremia and cell depletion in the bone marrow, among other things. The virus is spread easily via the respiratory route, is readily transmitted with close contact, and has a transmission rate with household contact approaching 50%. Nosocomial transmission of the virus has also been documented.⁶

What would happen if the blood supply were contaminated by a new pig virus which spread like parvovirus? FDA has admitted that such a scenario would be “disastrous.”

Given what is at stake here, and our history with AIDS,⁷ CRT recommends that blood products, which are retrospectively found to contain material from xenotransplant patients and/or their intimate

⁴ Equally shocking was the company’s admission that it had not kept a registry of the hundreds of patients it has treated since the 1980s. FDA appeared to have no knowledge of the situation and had obviously not enforced patient monitoring procedures, opening up the possibility that these patients may have already engaged in risky behaviors and/or donated blood. As happened during the AIDS crisis, and given some companies’ failure to track patients treated with their xenotransplant products, it may be impossible to locate infected individuals or those who may have had contact with infected individuals; and it may be impossible to determine the original source of infection.

⁵ CBERINFO online, March 28, 2002.

⁶ <http://www.aafp.org/afp/991001ap/1455.html>.

⁷ AIDS - which has claimed tens of millions of lives around the world - and the threat of CJD (“mad cow disease”) have already reduced the number of blood donors in the U.S., Canada and abroad.

contacts, be withdrawn from circulation immediately. Any other policy would be dangerous and short-sighted.

Lastly, in this guidance document the FDA makes certain biased statements which must be challenged.

The agency claims that “despite intensified efforts to enlarge the pool of human organ donors, there is a critical shortage of human organs available for transplant.” CRT contends, and reports confirm, that efforts to increase human organ donation have not been intense enough. A General Accounting Office report on organ donation (April 1998) found that the Health Care Finance Administration has not considered all available methods for determining, and thus increasing, the number of potential organ donors, suggesting that the number of available organs may be much higher than previously thought.⁸

An October 1999 Health and Human Services report to Congress stated that, “[b]ehavioral theories and models that have proved effective for large-scale behavior change related to other health issues such as preventing or reducing tobacco use, drinking and driving, and high cholesterol, have yet to be applied in a meticulous way to efforts to increase [human organ] donation.”⁹

Hence, a more appropriate and accurate statement would be that “efforts to enlarge the pool of human organs for donation need to be improved.”

Secondly, FDA claims that “scientific advances have begun to overcome the formidable immunologic barriers to the survival of animal transplants in humans.” This sounds like a quote from an industry press release. Scientists like Carl Hammer,¹⁰ Simon Crick,¹¹ M. E. Breimer,¹² and E. O. Schraa¹³ have described basic physiological, anatomic, biochemical, and mechanistic differences between pigs and humans which call into question the rationale for considering xenotransplantation as a safe or viable therapy in the first place. Hence, we find FDA’s statement to be vague, subjective, and potentially inaccurate.

Lastly, FDA claims that, if successful, “clinical [xenotransplantation] trials could provide another future therapeutic option for millions of insulin-dependent diabetic patients.” Again, this sounds like an industry press release. No mention is made of redirecting resources to perfecting *human* islet cell transplants, and yet several research teams are working on this promising approach, most notably the

⁸ General Accounting Office, Organ Donation: Assessing Performance of Organ Procurement Organizations, (GAO, Washington, DC, April 8, 1998).

⁹ Anon, Amendments to the Organ Procurement and Transplant Network (OPTN) Final Rule, Report to Congress: Organ Donation Program, October 20, 1999, Source: www.organdonor.gov/congress.htm.

¹⁰ Hammer C, et al.. Organs from animals for man. *Int Arch Allergy Immunol* 1998 May; 116 (1): 5-21; Hammer, C. Physiological obstacles after xenotransplantation. *Ann NY Acad Sci* 1998 Dec 30; 862: 19-27.

¹¹ Crick SJ, et al.. Anatomy of the pig heart: comparisons with normal human cardiac structure. *J Anat* 1998 Jul; 193 (Pt 1): 105-19.

¹² Breimer ME. Physiological incompatibilities in discordant xenotransplantation. *Transplantation Proceedings* 31 (1999): 905-908. Breimer lists “different physiological incompatibilities . . . in the pig to human species combination” in a table.

¹³ Schraa EO, et al. The fourth barrier. *Current Medical Research and Opinion* 15(4): 327-338, 1999.

Seattle Human Islet Transplantation Project¹⁴ and James Shapiro, et al., at the University of Alberta in Edmonton, Canada.¹⁵

In addition, according to the American Diabetes Association, “Type 2 diabetes [can] be prevented or delayed”¹⁶ through lifestyle modifications, such as a low-fat diet, and increased physical activity.¹⁷ Preventing diabetes would certainly be a much safer and cost-effective option than xenotransplantation.

We have previously stated our belief that, FDA’s current xenotransplant policy is based on containment, rather than prevention of infectious disease. CRT believes that if the FDA were truly interested in protecting public health and the blood supply, it would ban xenotransplantation immediately and explore a range of safer, more humane, and cost-effective alternatives. In the interim, **CRT strongly recommends that, at the very least, the FDA ban blood donations from all xenotransplant patients and their intimate contacts.**

Respectfully,

Alix Fano, MA
Director

On behalf of CRT’s 3 million members

¹⁴ Carol Smith. Seattle research group will try revised cell transplant technique. Seattle Post Intelligencer, August 16, 1999, p.A1. The article states that the Pacific Northwest Research Institute in Seattle is growing human islets in culture, while the Puget Sound Blood Center serves as an islet bank, isolating and storing islets for transplant programs on the West Coast. This could be a model for centers around the U.S.. See also Miyamoto M. Current progress and perspectives in cell therapy for diabetes mellitus. Hum Cell 2001 Dec; 14(4): 293-300, which discusses growing human pancreatic beta islet cells in vitro

¹⁵ www.joslin.harvard.edu/news/islet_transplant_july.shtml (July 2000), Joslin Part of Ten Site, Worldwide Clinical Trial of Islet Transplants Using Edmonton Protocol. More than 16 people with type 1 diabetes have had human islet transplants with minimal immunosuppressive therapy, using the “Edmonton protocol.” Two-thirds of them are insulin-free and the one-year insulin independence rate is 80%. Source: http://www.insulinfreetimes.org/01_fall/I_trials_2.htm.

¹⁶ American Diabetes Association, position statement. The Prevention or Delay of Type 2 Diabetes. *Diabetes Care* 25: 742-749, 2002.

¹⁷ Physicians Committee for Responsible Medicine with Patricia Bertron, Healthy Eating for Life to Prevent and Treat Diabetes, John Wiley & Sons, New York, 2002.