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Comments Regarding the Food and Drug Administration's Guideline:

“Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Close Contacts”

Published in the Federal Register, December 30, 1999

Docket No. 99D-5347

Comments submitted January 24, 2000

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

99D-5347

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CRT is an international health advocacy group composed of physicians, scientists, health care professionals, and public interest groups opposing animal-to-human organ and tissue transplantation, which poses a grave danger to human health because of the risk of transferring deadly animal viruses to the human population.

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Summary

Re: Docket No. 99D-5347

Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Close Contacts
Federal Register, December 30, 1999

The Campaign for Responsible Transplantation (CRT) is an international coalition of physicians, scientists and 77 public interest groups representing millions of people concerned about the public health risks inherent in xenotransplantation. We would like to comment on the draft guideline related to "indefinitely deferring" blood donations from xenotransplantation recipients and their "close contacts."

The FDA has acknowledged that "[X]enotransplantation may facilitate the transmission of known or as yet unrecognized agents to humans." In light of this, the proposed guideline is inadequate, short-sighted, and will not protect the U.S. blood supply as currently written.

The mere fact that this blood guideline is being proposed, demonstrates that xenotransplantation poses a threat to the public health and that previous draft guidelines from 1996 - which also recommended blood bans from patients - are being ignored.

FDA may be repeating mistakes it made while monitoring blood supplies during the AIDS crisis: by downplaying the risks of infection from pig viruses, suggesting weak blood donor screening strategies and regulatory actions, and by failing to offer a contingency plan in the event of a public health emergency.

The proposed guideline ignores the fact that, like "mad cow disease," symptoms of disease from a novel animal virus may not manifest themselves for decades after infection. At any given time, doctors and hospitals may determine that xenograft patients' close contacts are free of infection and able to give blood. But as with AIDS or CJD, these same individuals could develop a full-blown infection ten years down the road, with devastating consequences for the blood supply. This guideline also ignores that, as with swine flu, some infections may be transmitted to casual contacts. Xenograft patients could transmit zoonotic diseases, not only to close contacts, but also to casual contacts who may unknowingly donate blood while infected with a zoonotic agent.

As happened during the AIDS crisis, and given some companies' failure to track patients treated with their xenotransplant products, it may be virtually impossible to locate all infected individuals or those who may have had contact with infected individuals; and it may be impossible to determine the original source of infection.

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AIDS and the threat of CJD ("mad cow disease") have already reduced the number of blood donors in the U.S., Canada and abroad. FDA has acknowledged that if a xenotransplant-related virus entered the blood supply by mistake, the results would be "disastrous." And yet it is unclear how FDA plans to defer blood and plasma donations from xenograft patients and their contacts. Without clearly defined and standardized hospital procedures to prevent blood donations from these individuals, hospitals will be unable to safeguard the blood supply from zoonotic agents.

Only a national computerized name-based registry, listing the names and addresses of xenograft recipients and their contacts (pending a definition of who they are) would allow the identification of these individuals, to prevent them from donating blood. Such a registry, however, is plagued by numerous legal problems; 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, or if hospital procedures are not carried out correctly.)

The Institute of Medicine and the General Accounting Office have already cited the FDA for its weak oversight of the nation's blood supply. FDA has failed to provide appropriate oversight for human tissues infected with HIV and other viruses, for tracking and recall systems for defective medical devices, and medical implants. In 1996, the agency approved the use of a bioengineered plasma product that transmitted hepatitis A to hemophiliacs. We cannot afford any more public health disasters.

In CRT's view, FDA's current xenotransplant policy is based on containment, rather than prevention of infectious diseases. All xenograft guidelines, including this one, are being proposed in hindsight, because humans have been receiving cells, tissues and organs from animals for decades. Yet due to the absence of name-based registries for xenograft patients and their contacts, the lack of adequate tracking and monitoring of these individuals, and lack of enforcement of existing guidelines, it is possible that patients and their contacts may have already engaged in risky behaviors and/or donated blood. This is a frightening possibility.

If FDA were truly interested in protecting the blood supply, it would ban xenotransplantation immediately. If it does not, the agency will be playing Russian Roulette with the public's health, and may be held legally liable in the event of a public health crisis caused by a zoonotic agent.

Alix Fano, MA
Director
On behalf of CRT's 2.5 million members

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January 24, 2000

Re: Docket No. 99D-5347

Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Close Contacts
[Federal Register, Vol. 64, No. 250, December 30, 1999, pp.73562-3.]

To whom it may concern:

The Campaign for Responsible Transplantation (CRT) is an international coalition of physicians, scientists and 77 public interest groups representing millions of people concerned about the public health risks inherent in xenotransplantation. We would like to comment on the draft guideline related to "indefinitely deferring" blood donations from xenotransplantation recipients and their "close contacts" (Docket No. 99D-5347).

Introduction

First we would like to make the observation that this draft guideline is imbued with biased value judgements about the purported desirability of xenotransplantation. This despite the fact that the public has yet to be consulted about the technology's risks in a democratic forum; and that the advisory committee (SACX), which is to advise the current Secretary for Health and Human Services (HHS), Donna Shalala, on policy, has yet to be assembled.

Moreover, in 1996, the Organisation for Economic Cooperation and Development (OECD) stated that "[t]he economic impacts of the development of xenotransplantation have not been adequately addressed."¹ That is still true today. Neither the Food and Drug Administration nor its parent agency, HHS, have prepared a cost-benefit analysis to determine the true cost of xenotransplant procedures and the economic impact the widespread application of the technology would have on our health care system.

The OECD also stated that the development of xenotransplantation "may conflict with efforts to keep medical costs down; may contribute to the development of multi-tier medicine; may conflict with efforts to develop better approaches to preventive medicine; may discourage donation of [human] organs for allotransplantation; [and] may not be consistent with striving for humane and fair medicine."²

¹ Elettra Ronchi, Biotechnology Unit, Organisation for Economic Cooperation and Development, *Advances in Transplantation Biotechnology and Animal to Human Organ Transplants (Xenotransplantation)*, (OECD, Paris, 1996), p.78.

² Elettra Ronchi, (OECD, Paris, 1996), p.79.

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According to published reports,³ and contrary to statements made in this draft guideline, “intensified efforts to enlarge the pool of human organ donors” have not been exhaustive by any means. The merits of “presumed consent” legislation, which has increased organ donation rates in other countries,⁴ have not been examined in the U.S.. In our opinion, therefore, it is entirely inappropriate for the FDA to promote xenotransplantation as a desirable technology.

In addition, in this guideline, the FDA acknowledges that baboon Cytomegalovirus (BCMV) was “detected in stored blood and duodenal samples obtained from a recipient of a baboon liver in a xenotransplantation procedure performed several years earlier.” Given this discovery, and the known virulence of nonhuman primate viruses, the FDA must now revisit the guidance it issued in April 1999 (Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans) and ban the use of nonhuman primates in xenotransplant procedures outright. To wait for the collection of further “scientific information” is unnecessary and merely leaves the door open for future use of these species. This is blatantly irresponsible.

CRT has already stated its belief that pigs pose just as great a risk as nonhuman primates, and perhaps more so because their cells and tissues have been more widely transplanted into humans. This despite the fact that “our understanding of the retrovirology of xenotransplant source animals is incomplete,” and that “little or nothing is known about the pathogenic potential of endogenous retroviruses introduced directly into other species.”⁵

At a January 13, 2000 meeting of the Xenotransplant Subcommittee in Gaithersburg, Maryland, Dr. Prem Paul, a veterinary researcher at Iowa State University, warned that new pig viruses were continually being discovered; they had not been extensively studied; and the potential existed for them to mutate and infect humans. British veterinary pathologist David Onions stated that mammalian cells had not been extensively studied. He cautioned that, besides the porcine endogenous retroviruses (PERVs), porcine parvovirus - which can change hosts, escape inactivation treatments, and which has already been found in Porcine Factor 8, used to treat hemophiliacs - could represent a potential threat to the blood supply. He concluded that “some human cells will likely be infected in a xenotransplant.”

In this guideline, the FDA confirms that “[t]he clinical consequence of the introduction of endogenous retroviruses into immunocompromised human hosts remains, in most instances, undefined.”

We are further stunned that, similarly to the 1996 Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, this guideline blatantly acknowledges the grave public health risks posed by xenotransplantation:

³ R. W. Evans, “The Potential Supply of Organ Donors: An Assessment of the Efficacy of Organ Procurement in the United States,” *JAMA*, Vol. 267 (1992): 239-46; General Accounting Office, *Organ Donation: Assessing Performance of Organ Procurement Organizations*, (GAO, Washington, DC, April 8, 1998).

⁴ I. Kennedy, et al., “The Case for “Presumed Consent” in Organ Donation,” *The Lancet*, Vol. 351 (May 30, 1998): 1650-2.

⁵ Jonathan P. Stoye, et al., “Endogenous Retroviruses: A Potential Problem for Xenotransplantation,” *Annals of the New York Academy of Sciences*, Vol. 862 (1998): 68.

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"[X]enotransplantation may facilitate the 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. . . . endogenous retroviruses may not be eliminated from source animals by herd health surveillance and screening programs. . . . Xenotransplantation provides a unique environment for adaptation and cross-species transmission of infectious agents. . . ."

By making such statements and then allowing the application of xenotransplantation, the FDA is acting irrationally: *"On [the] one hand, the real implications of possible harm to people are recognized, while on the other, the need for knowledge, without reference to human consequences, seems to prevail."*⁶

That said, we will now comment on the guideline itself.

New Blood Guideline Reflects Weak Oversight of Xenotransplantation: Proposed Measures Are Inadequate and Vulnerable to Error

The mere fact that this blood guideline is being proposed, demonstrates that xenotransplantation poses a threat to the public health. (The guideline suggests that xenograft patients and their "close contacts" (who remain undefined)⁷ should be "indefinitely deferred" from donating blood or tissue because "these individuals are theoretically at risk of acquiring zoonoses, and of transmitting them" (see Background); and it suggests labeling xenotransplant products used in research and manufacturing as 'Biohazards' (see Labeling of Products Distributed for Research or Intended for Further Manufacturing Into Non-Injectable Products.)

The guideline is also evidence that previous draft guidelines from 1996 - which also recommended blood bans from patients - are being ignored. (CRT is concerned that FDA does not seem to have a mechanism in place for determining whether previous guidelines are being followed.)

By revealing that health care workers, laboratory personnel and other individuals may unwittingly become infected with zoonotic agents by "accidental needlestick" for example (see Donor Deferral), and implying that whole blood and blood components derived from xenograft recipients could accidentally wind up in the blood supply, (see Blood Product Quarantine and Withdrawals) this guideline exposes the

⁶ Suzanne D. Fullbrook, M.B. Wilkinson, "Animal to Human Transplants: The Ethics of Xenotransplantation (1)," *British Journal of Theatre Nursing*, Vol. 6, No. 2 (May 1996): 31.

⁷ The definition of "close contacts" remains undefined for fear that too broad a definition could exclude a large number of potential blood donors. At the same time, discussions at the January 13th meeting revealed that FDA was considering allowing xenotransplant patients themselves to educate "close contacts" about the risks of infection from xenotransplantation. This would be dangerous and - considering past experience with the AIDS crisis - reflects a poor understanding of human psychology.

probability of human error. "To err is human."⁸ But given the acknowledged risks posed by xenotransplantation, human error, in this case, could have grave consequences.

At the January 13th Xenotransplant Subcommittee meeting, Dr. Andrew Dayton of the FDA's Division of Transfusion Transmitted Diseases, and architect of the blood guideline, acknowledged that if a xenotransplant-related virus entered the blood supply by mistake, the results would be "disastrous" and the necessary withdrawal of contaminated blood products would cause serious blood shortages.

Yet at the meeting, FDA's current policy was revealed to be mercurial. After hearing testimony from the blood industry, the Subcommittee voted to eliminate three questions that were going to be added to blood questionnaires to prevent xenotransplant recipients and their "close contacts" from donating blood. Just two weeks earlier, these questions were a key component of the FDA's blood guideline. The agency's reliance upon such questions as a method for protecting the blood supply from novel zoonotic viruses was a troubling concept in and of itself.⁹ The Institute of Medicine (IOM) has criticized "[the use of] questions to eliminate high-risk groups." According to IOM, they are limited in their ability to prevent the transmission of infectious agents through the blood supply, and their use is reflective of "a lack of consensus about the magnitude of the threat" posed by such agents.¹⁰

IOM has also criticized FDA for its decision to handle blood recalls on a case-by-case basis.¹¹ It would be foolish, therefore, to allow "medical directors" to determine blood donor deferrals on a "case-by-case basis." Because xenotransplantation proponents would like to see tens if not hundreds of thousands of patients receive xenotransplant products, such a system would quickly become unmanageable.

It is unclear now - absent the three questions that were eliminated from the guideline at the January 13th meeting, absent a xenotransplant patient registry (see below), and absent any explanation about how hospital staff would implement the proposed precautionary measures - how the FDA plans to defer blood and plasma donations from these individuals.

As it is, blood supplies are continually at risk due to "human error, technological limitations of state-of-the-art tests, and the biological nature of the product itself."¹² Without clearly defined and standardized hospital procedures to prevent blood donations from xenograft patients and their "close

⁸ *To Err is Human* - is the title of an Institute of Medicine report released in November 1999, which found that medical errors kill between 44,000 and 98,000 people in U.S. hospitals each year - more than die from highway accidents, breast cancer, or AIDS. Institute of Medicine, *To Err is Human: Building a Safer Health System* (National Academy Press, Washington, DC, November 1999).

⁹ Moreover, the General Accounting Office has stated that "the lack of a uniform donor questionnaire allows variability in donor screening." General Accounting Office, *Blood Supply: FDA Oversight and Remaining Issues of Safety*, (GAO, Washington, DC, February 25, 1997.)

¹⁰ Institute of Medicine, *HIV and the Blood Supply: An Analysis of Crisis Decisionmaking*, (National Academy Press, Washington, DC, 1995), p.3.

¹¹ Institute of Medicine, (1995), p.7.

¹² General Accounting Office, (February 25, 1997.)

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contacts," these pre-existing risks will be heightened, and hospitals will be unable to safeguard the blood supply from zoonotic agents.

The ramifications of contaminated blood supplies have been deadly. Between 1994 and 1996, some 40,000 people received blood that had been improperly tested for HIV,¹³ hepatitis B and C, and HTLV (Human T Lymphotropic Virus). The Manhattan Blood Center tried to reach patients through newspaper and radio announcements,¹⁴ though it is unknown how successful this outreach effort was. More recently, U.S. and Canadian health authorities announced an indefinite ban on blood donations from citizens who spent six months or more in Britain since 1980 (about 285,000 Americans and 25,000 Canadians), for fear of Creutzfeldt Jakob "mad cow" Disease (CJD).¹⁵ (According to a report by an official EU (European Union) scientific committee, up to 400,000 people could be infected by a single cow with BSE (bovine spongiform encephalopathy) entering the food chain.)¹⁶

Because it takes years, or possibly decades, before symptoms of CJD appear in humans, authorities are concerned that many people may be carrying the disease without knowing it. If the disease can be spread by blood, carriers who are blood donors may be unknowingly infecting large blood pools. There is no test to detect traces of the disease. According to an official of the American Red Cross, "this will indeed impact the American blood supply."¹⁷

Could an as yet unknown porcine virus already be lurking in the blood supply, undetected by current commercial testing methods? HIV nucleic acid detection tests were not commercially available when the CDC revised its AIDS case definition in 1993. Today, blood banks can use nucleic acid testing (NAT) to screen for hepatitis or HIV, but NAT cannot detect a brand new virus, only one that is related to an existing virus. A novel zoonotic agent, therefore, could slip through the cracks. If it is discovered in the blood supply one year, five years, or ten years from now, it would have a major impact on the blood supply and the health care system. It would be virtually impossible (as it was during the AIDS crisis) to locate all infected individuals, or those who may have had contact with infected individuals. More importantly, it may be impossible to determine the original source of infection.

The complex nature of any surveillance infrastructure and the unpredictable nature of viruses will exacerbate the problem.

¹³ In the 1980s, contaminated blood-clotting products infected thousands of hemophiliacs with HIV. James Dao, "Pataki Signs Bill Letting Hemophiliacs Sue Companies Over Blood-Clotting Products," *The New York Times*, December 2, 1997.

¹⁴ Verena Dobnik, "Blood Bank Warns of Improper Tests," Associated Press, December 3, 1998.

¹⁵ In 1998, 350 people were injected with a blood product made with plasma from a British donor who later died of Creutzfeldt-Jakob Disease. Anon, "350 Injected With Mad Cow Tainted Blood," Associated Press, May 17, 1998. The UK destroyed nearly all blood plasma donated in Britain due to concerns about the spread of "mad cow disease." Steve Stecklow, "Mad Cow Fear Leads UK to Destroy Parts of All Donated Blood," *The Wall Street Journal*, November 25, 1998, p.A1.

¹⁶ Dick Ahlstrom, "One BSE Cow Can Infect 400,000 People, Says Report," *Irish Times*, 6 January 2000.

¹⁷ Steve Stecklow, "Mad Cow Fears Lead to Blood Ban in U.S.," *The Wall Street Journal*, August 18, 1999, p.B6.

There is another important point to consider. Because humans have been receiving cells, tissues and organs from animals for decades, this and other xenograft guidelines are being proposed in hindsight.

In fact, at the January 13th Xenotransplant Subcommittee meeting, Genzyme, a Cambridge-based biotech company, described how it had been treating about 100 burn patients per year since 1987 with a xenotransplant product called Epicel, oddly regulated as a device.¹⁸ Most shocking was the company's admission that it had not kept a registry of the patients it treated, nor followed up to see whether any of them might have developed signs of illness or infection. Genzyme said it would be "impractical" to try to find these patients. The FDA seemed to have no knowledge of this situation.

Presumably, xenotransplant patient registries – if they existed - would list the names and addresses of patients and their "close contacts." (The possibility of aerosolized disease transmission to casual contacts, à la swine flu, seems to have been dismissed by FDA). Such patient registries clearly do *not* exist however; and it is possible that surviving xenograft patients and/or their "close contacts" may have already engaged in risky behaviors and/or donated blood or plasma while unknowingly infected with a new zoonotic virus. This is a frightening possibility.

Lessons to be Learned From the AIDS Crisis

It is troubling that, in attempting to regulate xenotransplantation, the FDA could be repeating mistakes it made during the AIDS crisis – mistakes which compromised the safety of the nation's blood supply.

In its 1995 report, *HIV and the Blood Supply*, the IOM revealed "several weaknesses in the FDA's regulatory approach to blood safety issues,"¹⁹ as well as "an important weakness in the [blood system's] ability to deal with a new threat that was characterized by substantial uncertainty."²⁰

IOM stated that "[m]any blood bank officials during this period publicly denied that AIDS posed any significant risk to blood recipients,"²¹ and when confronted with new information about disease risks, the FDA failed to change its blood safety policies despite opportunities to do so. The report cited a "failure of leadership" which led to "less than effective donor screening, weak regulatory actions, and insufficient communication to patients about the risks of AIDS,"²² as well as decisionmaking compromised by "personal or institutional biases."²³

¹⁸ The company uses 3T3 mouse cells to grow layers of human skin, which are then applied to the patient. The mouse cells are allegedly irradiated to prevent them, and any viruses, from proliferating; though when pressed at the meeting, Genzyme's President admitted that the company was still assessing the efficacy of its irradiation method. Moreover, it had not performed FDA-required tests to determine whether its mouse cells could infect human cells *in-vitro*.

¹⁹ Institute of Medicine, (1995), p.7

²⁰ *Ibid.*, p.2.

²¹ *Ibid.*, p.9.

²² *Ibid.*, p.11

²³ *Ibid.*

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At the January 13th meeting, some members of the Xenotransplant Subcommittee, as well as industry representatives, seemed intent on downplaying the threat of infection posed by pig and mouse viruses.²⁴ It was even suggested by FDA that xenotransplant patients who had had ex-vivo exposures to pig cells, as well as close contacts of patients treated with Genzyme's Epicel product, would not necessarily need to be deferred from donating blood.

Similarly in the 1980s, the FDA "accepted with little question estimates that the risk of AIDS was low²⁵ . . . [and] . . . "preference for the status quo under the prevailing conditions of uncertainty and danger led decisionmakers to underestimate the threat of AIDS for blood recipients . . . Prevailing assumptions about medically acceptable risks . . . led to complacency and a failure to act with sufficient concern upon reports of a new infectious risk,"²⁶ (i.e. PERVs). Research into ways to safeguard the blood supply "was not pursued vigorously."²⁷ Moreover, "when confronted with a range of options for using donor screening and deferral to reduce the probability of spreading HIV through the blood supply, blood bank officials and federal authorities chose the least aggressive option that was justifiable."²⁸ In our view, the FDA is doing this again vis-a-vis xenotransplantation.

The IOM report concluded that, given the magnitude of the risks, blood safety operations could not be governed by "ordinary standard operating procedures;" that it was the Public Health Service's responsibility to "plan what it will do if there is a threat to the blood supply;"²⁹ and it recommended the establishment of "a no-fault compensation system for individuals who suffer adverse consequences from the use of [contaminated] blood and blood products."³⁰

The current blood guideline does not include a contingency plan, or a compensation plan, to address public health emergencies that might arise as a result of xenotransplantation.

Previous Problems With FDA Oversight of the Blood Supply

In addition to the IOM report of 1995, several General Accounting Office (GAO) documents from 1997 and 1998 have revealed problems with FDA's oversight of the nation's blood supply, (as well as acts of negligence by blood product manufacturers). These problems have resulted in blood product withdrawals and shortages, and have led to public health crises.³¹

Among the problems cited by GAO included:

²⁴ This despite the fact that companies may not be using the most up-to-date technologies to screen for such viruses; that one cannot screen for unknown viruses; and that some viruses may remain latent for years before producing signs of disease.

²⁵ Institute of Medicine, (1995), p.4.

²⁶ Ibid., p.8.

²⁷ Ibid., p.4.

²⁸ Ibid., p.6.

²⁹ Ibid., p.10.

³⁰ Ibid., p.13.

³¹ General Accounting Office, (February 25, 1997); General Accounting Office, *Blood Safety: Enhancing Safeguards Would Strengthen the Nation's Blood Supply*, (GAO, Washington, DC, June 5, 1997); Bernice Steinhardt, Director, Health Services Quality and Public Health Issues, *Blood Plasma Safety: Plasma Product Risks and Manufacturers' Compliance*, before the Human Resources Subcommittee, House Committee on Government Reform and Oversight, September 9, 1998.

- The lack of mandatory deferral notification allows some blood donors who have tested positive for viruses to unwittingly attempt donation again
- Blood facilities are not required to remove from their inventory blood from donors who have subsequently tested positive for viral infections
- Not all recipients of virally contaminated blood are notified, which may keep them from seeking treatment and allows them to transmit disease. *(As a parallel to FDA's lackadaisical attitude towards tracking patients exposed to Genzyme's Epicel product and other xenotransplant products, the IOM noted that, during the AIDS crisis, the FDA delayed for years a formal decision to trace recipients of transfusions from donors who were later found to be infected with HIV.)*³²
- Untested units donated for self-use may inadvertently be used for unintended recipients
- FDA has been slow to investigate error and accident reports that may warrant a recall of blood and/or blood products
- Only a small proportion of distributed intravenous immune globulin – about 1.1% - has been removed from the market as a result of recalls or withdrawals
- Only 5% of the vials of plasma products that were recalled or withdrawn have been retrieved to date; while additional quantities may still be retrieved, a portion of these products have already been transfused or are otherwise irretrievable
- FDA does not require unlicensed blood facilities to report errors and accidents
- FDA has not fully monitored the quality of blood products derived from unlicensed facilities, which produce 10% of the nation's blood
- FDA's inspections for licensed and unlicensed facilities appear to be inconsistent in focus, scope, and documentation
- Inspections are often not conducted within time periods set by FDA's own guidelines
- FDA does not maintain a central repository for inspection reports and, thus, does not examine national trends
- There is confusion within the blood industry regarding the interpretation of FDA blood policies and guidelines

CRT does not know whether these problems have been corrected. Even if they have - which is unlikely given the recentness of the findings and the magnitude of the problems – these data demonstrate system-wide problems with FDA oversight of the nation's blood supply.

FDA has also failed to provide oversight for human tissues infected with HIV and other viruses,³³ was cited for "weak oversight" of tracking and recall systems for defective medical devices,³⁴ and most

³² Institute of Medicine, (1995), p.7.

³³ General Accounting Office, *Human Tissue Banks: FDA Taking Steps to Improve Safety but Some Concerns Remain*, (GAO, Washington, DC, December 1997); Meredith Wadman, "FDA Fails to Keep Track of Transplant Patients," *Nature*, Vol. 391 (22 January 1998): 315.

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recently medical implants.³⁵ In 1996, FDA approved the use of a bioengineered plasma product that transmitted hepatitis A to several hemophiliacs.³⁶ How can the public have confidence in the agency's ability to successfully implement the proposed blood guideline, oversee xenotransplantation in general, and protect the public health?

Recommendations

In light of experiences with AIDS and CJD, and weak FDA oversight of blood supplies and other patient products, the establishment of a national name-based registry of all patients, dead or alive, who have heretofore received xenotransplants, as well as their "close contacts," and relevant health care personnel, would provide the only hope for preventing blood donations from these individuals. If we are unwilling to enforce such a surveillance system through legislation, then we must acknowledge that xenotransplantation poses unacceptable risks to the blood supply and to the public health.

Washington and Texas have implemented HIV reporting by patient name to enable public health follow-up; and the Centers for Disease Control has concluded that "name-based methods for collecting and reporting public health data provide the most feasible, simple, and reliable means for ensuring timely, accurate and complete reporting of persons in whom HIV infection or AIDS has been diagnosed."³⁷

Shockingly, although xenotransplantation could cause an AIDS-like epidemic,³⁸ xenotransplant patient registries do *not* exist.

Such registries have their share of problems, however - they are invasive of privacy and restrictive of liberty; their procedures cannot be legally enforced; they are expensive to set up and manage; they are vulnerable to hackers,³⁹ they deter people, even those at high risk of infection, from seeking testing and registering with public health authorities; and they will always be vulnerable to human error (i.e. if patients marry, change their names, relocate, or if hospital procedures are not carried out correctly).

³⁴ General Accounting Office, *Medical Devices: FDA Can Improve Oversight of Tracking and Recall Systems*, (GAO, Washington, DC, September 24 1998).

³⁵ Rita Rubin, "A Body of Work in Spare Parts: Implants Abound Though Quality Control Doesn't," *USA Today*, January 13, 2000, p.D1.

³⁶ Anon, "FDA: Clotting Factor Linked to Hepatitis A Cases," *USA Today* online, January 15, 1996.

³⁷ Other states use a confidential system for name-based case reporting, or a code-based system. Patricia L. Fleming, et al., "Guidelines for National Human Immunodeficiency Virus Case Surveillance . . ." *MMWR Recommendations and Reports*, December 10, 1999/48(RR13); 1-28. Source: www.cdc.gov/EPO/MMWR/preview/mmwrhtml/RR4813a1.htm.

³⁸ Anon, "Animal-Organ Transplants Could Lead to New AIDS, Group Warns," Reuters, March 19, 1998; Dominic C. Borie, et al., "Microbiological Hazards Related to Xenotransplantation of Porcine Organs into Man," *Infection Control and Hospital Epidemiology*, Vol. 19, No. 5 (May 1998): 356, 359; Frederick A. Murphy, "The Public Health Risk of Animal Organ and Tissue Transplantation into Humans," *Science*, Vol. 273 (August 1996): 746-7.

³⁹ Hackers claim that they could shut down the entire Internet in less than 30 minutes, and say that no computer system is invulnerable to attack. Kevin Newman, "Elite Hackers Expose All," ABCNEWS.com, December 20, 1999. Source: http://abcnews.go.com/onair/worldnewstnight/wnt_991220_cl_10pht_feature.htm.

Frederickson writes, "A National Registry in which information about xenotransplant recipients is archived raises substantive Fifth and Fourteenth Amendment due process issues: individuals' privacy and the right to be free from government intrusion could be encroached. Arguably, the public health concerns of the unknown zoonoses, and their epidemic potential, would warrant this intrusion into the privacy of xenotransplant recipients. Such intrusion may give rise to other issues of government action working a deprivation of liberty."⁴⁰

Chae and Cooper write, "Congress will face the extremely difficult question of how to enforce regulations that will undoubtedly require compliant behavior on the part of XTx [xenotransplant] patients, their family members, friends, and hospital staff. Issues such as the regulation of US citizens who receive a XTx operation abroad . . . patient compliance with follow-up, and enforcement of the monitoring of the patient's family and social contacts will certainly challenge the imagination and authority of the PHS [Public Health Service]."⁴¹

A neglected issue is the cost of such a surveillance system or registry. Frederickson writes, "Even if, arguendo, a National Registry is within the purview of FDA's regulatory scope and does not limit the privacy interest any more than is necessary, such a program is costly and difficult to manage. The costs associated with administering the National Organ Transplant Act are nearly \$2,800,000 a year. Already overburdened and underbudgeted, FDA is not in a position to accept responsibility for creating a National Registry without congressional approval and budgetary backing."⁴²

Indeed, xenotransplantation is already causing a plethora of problems and extra work for numerous branches and agencies of the federal government, and will consume a substantial amount of scarce public resources that CRT believes would be better spent elsewhere.⁴³ CRT has been asking FDA and/or HHS to address the cost of xenotransplantation since 1998, and both have yet to do so. When asked, at the January 13th meeting, about the issue of liability in the event of a xenozoonosis, the FDA's Dr. Phil Noguchi said that he would not address the issue.

Conclusion

The FDA has acknowledged that "[X]enotransplantation may facilitate the transmission of known or as yet unrecognized agents to humans." In light of this, the proposed guideline to bar blood donations from xenotransplantation recipients, their "close contacts" (who remain undefined), and relevant health care personnel is inadequate, short-sighted, and will not protect the U.S. blood supply as currently written.

⁴⁰ Jodi K. Frederickson, "He's All Heart . . . and a Little Pig Too: A Look at the FDA Draft Xenotransplant Guideline," *Food and Drug Law Journal*, Vol. 52, No. 4, (1997): 442.

⁴¹ Sanders J. Chae, David K.C. Cooper, "Legal Implications of Xenotransplantation," *Xenotransplantation*, Vol. 4 (1997): 136.

⁴² *Ibid.*

⁴³ Providing basic health care to the 50 million Americans who lack it; increasing human organ donation; aggressively implementing preventive medicine programs to prevent disease and shrink the number of patients on transplant waiting lists.

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The mere fact that this blood guideline is being proposed, demonstrates that xenotransplantation poses a threat to the public health and that previous draft guidelines from 1996 - which also recommended blood bans from patients - are being ignored.

FDA may be repeating mistakes it made while monitoring blood supplies during the AIDS crisis: by downplaying the risks of infection from pig viruses, suggesting weak blood donor screening strategies and regulatory actions, and by failing to offer a contingency plan in the event of a public health emergency.

The proposed guideline ignores the fact that, like "mad cow disease," symptoms of disease from a novel animal virus may not manifest themselves for decades after infection. At any given time, doctors and hospitals may determine that xenograft patients' close contacts are free of infection and able to give blood. But as with AIDS or CJD, these same individuals could develop a full-blown infection ten years down the road, with devastating consequences for the blood supply. This guideline also ignores that, as with swine flu, some infections may be transmitted to casual contacts. Xenograft patients could transmit zoonotic diseases, not only to close contacts, but to casual contacts who may unknowingly donate blood while infected with a zoonotic agent.

As happened during the AIDS crisis, and given some companies' failure to track patients treated with their xenotransplant products, it may be virtually impossible to locate all infected individuals or those who may have had contact with infected individuals; and it may be impossible to determine the original source of infection.

AIDS and the threat of CJD ("mad cow disease") have already reduced the number of blood donors in the U.S., Canada and abroad. FDA has acknowledged that if a xenotransplant-related virus entered the blood supply by mistake, the results would be "disastrous." And yet it is unclear how FDA plans to defer blood and plasma donations from xenograft patients and their contacts. Without clearly defined and standardized hospital procedures to prevent blood donations from these individuals, hospitals will be unable to safeguard the blood supply from zoonotic agents.

Only a national computerized name-based registry, listing the names and addresses of xenograft recipients and their contacts (pending a definition of who they are) would allow the identification of these individuals, to prevent them from donating blood. Such a registry, however, is plagued by numerous legal problems; 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, or if hospital procedures are not carried out correctly.)

The Institute of Medicine and the General Accounting Office have already cited the FDA for its weak oversight of the nation's blood supply. FDA has failed to provide appropriate oversight for human tissues infected with HIV and other viruses, for tracking and recall systems for defective medical devices,

and medical implants. In 1996, the agency approved the use of a bioengineered plasma product that transmitted hepatitis A to hemophiliacs. We cannot afford any more public health disasters.

In CRT's view, FDA's current xenotransplant policy is based on containment, rather than prevention of infectious diseases. All xenograft guidelines, including this one, are being proposed in hindsight, because humans have been receiving cells, tissues and organs from animals for decades. Yet due to the absence of name-based registries for xenograft patients and their contacts, the lack of adequate tracking and monitoring of these individuals, and lack of enforcement of existing guidelines, it is possible that patients and their contacts may have already engaged in risky behaviors and/or donated blood. This is a frightening possibility.

If FDA was truly interested in protecting the blood supply, it would ban xenotransplantation immediately. If it does not, the agency will be playing Russian Roulette with the public's health, and may be held legally liable in the event of a public health crisis caused by a zoonotic agent.

Sincerely,



Alix Fano, MA

Director

On behalf of CRT's 2.5 million members

Blood Supply: FDA Oversight and Remaining Issues of Safety (Chapter Report, 02/25/97, GAO/PEMD-97-1).

Pursuant to a congressional request, GAO evaluated the Food and Drug Administration's (FDA) "layers of safety" that provide the framework for regulating and monitoring the U.S. blood industry, focusing on the actual and potential vulnerabilities in the layers of safety that may present a threat to the public health.

GAO found that: (1) the transmission of human immunodeficiency virus (HIV) by transfusion decreased dramatically after HIV testing for donors was introduced in 1985, and more and better tests for other diseases also have reduced the risks from blood transfusions; (2) while the blood supply is very safe, no amount of federal regulation can entirely eliminate blood-transfusion risks because of human error, technological limitations of state-of-the-art tests, and the biological nature of the product itself; (3) within the overlapping layers of safety, GAO found areas where FDA can take action that would further improve the safety of the blood supply: (a) the lack of a uniform donor questionnaire allows variability in donor screening; (b) the lack of mandatory deferral notification allows some donors who have tested positive for viruses to unwittingly attempt donation again; (c) untested units donated for self-use may inadvertently be used for unintended recipients; and (d) FDA has been slow to investigate error and accident reports that may warrant a recall; (4) FDA does not require unlicensed facilities, those that do not engage in the sale, barter, or exchange of blood products across state lines, to report errors and accidents; (5) because unlicensed facilities constitute more than two thirds of all blood facilities that, together, produce 10 percent of the nation's blood, FDA has not fully monitored the quality of this portion of blood products; (6) FDA's inspections for both licensed and unlicensed blood facilities appear to be inconsistent in focus, scope, and documentation; (7) in addition, these inspections are often not conducted within time periods set by FDA's own guidelines; (8) FDA does not maintain a central repository for inspection reports and, thus, does not examine national trends; and (9) GAO's survey results also indicated confusion within the blood industry regarding the interpretation for FDA policy guidance and regulations.

----- Indexing Terms -----

REPORTNUM: PEMD-97-1
 TITLE: Blood Supply: FDA Oversight and Remaining Issues of Safety
 DATE: 02/25/97
 SUBJECT: Acquired immunodeficiency syndrome
 Infectious diseases
 Safety regulation
 Health hazards
 Inspection
 Testing
 Reporting requirements
 Product safety
 Medical supplies
 Quality control
 IDENTIFIER: Medicare Program
 Medicaid Program
 AIDS
 FDA Program Oriented Data System
 FDA Error and Accident Reporting System

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 ** GAO report. Delineations within the text indicating chapter **

Blood Safety: Enhancing Safeguards Would Strengthen the Nation's Blood Supply (Testimony, 06/05/97, GAO/T-HEHS-97-143).

GAO discussed its two reports on the safety of the nation's blood supply, focusing on: (1) the current risks of blood transfusion; (2) the content and quality of data collected to assess these risks; and (3) the Food and Drug Administration's (FDA) layers of safety and their ability to ensure the safety of the nation's blood supply.

GAO noted that: (1) its analysis of current risks from transfusion showed that, while the nation's blood supply is safer today than at any time in recent history, some risk remains, even if all the safeguards available work perfectly; (2) GAO also found several vulnerabilities and gaps in current procedures which, if eliminated, would provide greater assurance of safety for the nation's blood supply; (3) the most serious of these problems follow: (a) not all donors who test positive for certain viruses are notified, which means that they can attempt to donate again and also may go without treatment; (b) similarly, not all recipients of virally contaminated blood are notified, which may keep them from seeking treatment and also allow them to transmit the disease; (c) blood facilities are not required to remove from their inventory blood from donors who have subsequently tested positive for viral infections; (d) unlicensed blood facilities that, together, produce 10 percent of the nation's blood do not have to submit to FDA error and accident reports that may signal the need to recall potentially contaminated units of blood; (e) FDA's investigations of error and accident reports that warrant a recall take a long time and increase the risk that units will have been transfused before a recall is accomplished; and (f) finally, FDA's inspections of blood facilities are inconsistent in focus, scope, and documentation; and (4) GAO's reports contained a number of recommendations to the Secretary of Health and Human Services to eliminate these weaknesses in the quality assurance system for the blood supply.

----- Indexing Terms -----

REPORTNUM: T-HEHS-97-143
 TITLE: Blood Safety: Enhancing Safeguards Would Strengthen the
 Nation's Blood Supply
 DATE: 06/05/97
 SUBJECT: Product safety
 Infectious diseases
 Quality control
 Testing
 Acquired immunodeficiency syndrome
 Safety regulation
 Health hazards
 Inspection
 Reporting requirements
 Medical supplies
 IDENTIFIER: AIDS
 FDA Error and Accident Reporting System

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Blood Safety: Recalls and Withdrawals of Plasma Products (Testimony, 05/07/98, GAO/T-HEHS-98-166).

GAO discussed the amount of plasma products, and in particular, the amount of intravenous immune globulin (IVIG), that was being lost due to removal of products from the market, focusing on the: (1) number of recent product recalls and withdrawals; (2) reasons for these actions; (3) different types of plasma products affected; (4) amount of product that has been returned as a result of these actions; and (5) current shortage of IVIG of reducing the number of donors for each plasma product.

GAO noted that: (1) the data showed that only a small proportion of distributed IVIG--about 1.1 percent--has been removed from the market as a result of recalls or withdrawals; (2) however, only 5 percent of the vials of plasma products that were recalled or withdrawn has been retrieved to date; (3) while additional quantities might still be retrieved, some portion of these products has already been transfused or is otherwise unretrievable; (4) further, changes to reduce the number of donors in each product appear unrelated to the current shortages; (5) during the period GAO reviewed, 11 manufacturers reported to the Food and Drug Administration (FDA) that they undertook a total of 12 recalls (affecting 33 lots of 7 types of plasma products) and 38 withdrawals (affecting 1,001 lots of 10 types of products); (6) the reasons for the product recalls varied, but generally they related to specific manufacturing errors resulting in problems in product potency, sterility assurance, or incorrect labeling; (7) the product withdrawals were all related to donors who were diagnosed with Creutzfeldt-Jakob disease (CJD) or were considered to be at increased risk for CJD; (8) as reported to FDA, the proportion of IVIG vials retrieved following a recall was 15 percent, which amounted to less than 1 percent of total IVIG distributed in 1997; (9) in total, about one-third, or 38 percent, of the number of vials of all plasma products recalled has actually been retrieved from distribution or known to be destroyed; (10) the proportion of distributed products retrieved following a withdrawal has been much lower; (11) data from the plasma product manufacturers showed 6 percent of the vials of IVIG that were withdrawn to actually have been recovered, representing 1 percent of the total product distributed in 1997; (12) for other plasma products, the proportion of distributed vials retrieved following a withdrawal was 2 percent; and (13) manufacturers also claim that their production of IVIG was reduced by 5 to 10 percent in 1997 because they had to quarantine or destroy plasma because of CJD risk, but these amounts cannot be verified.

----- Indexing Terms -----

REPORTNUM: T-HEHS-98-166
TITLE: Blood Safety: Recalls and Withdrawals of Plasma Products
DATE: 05/07/98
SUBJECT: Product recalls
Health hazards
Neurological diseases
Product safety
Health care services
Medical supplies

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