DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of the Secretary
Office of Public Health and Science

Assistant Secretary for Health
Surgeon General
Washington, D.C. 20201

DEC 7 1999

Mr. Andrew Kimbrell, Esq., et al.
International Center for Technology Assessment
310 D Street, N.E.
Washington, DC 20002

Re: Docket Number: 98P-1147

Dear Mr. Kimbrell:

This letter is in response to the citizen petition, filed on December 10, 1998, submitted to Donna E. Shalala, Secretary of Health and Human Services, requesting that the Department of Health and Human Services (DHHS) take the following actions:

1. Initiate rulemaking proceedings to prohibit xenotransplantation;
2. Issue an environmental assessment (EA) or an environmental impact statement (EIS) under the National Environmental Policy Act (NEPA); and,
3. Grant such other relief as the Secretary deems just and proper.

The petition asserts that the Department of Health and Human Services arbitrarily and capriciously issued the Draft PHS Guideline on Infectious Disease Issues in Xenotransplantation (Draft Guideline) in violation of the Public Health Service Act by not considering issues of safety, efficacy, or cost of transplantation, nor the social, ethical and legal implications of xenotransplantation. The petition also alleges that DHHS violated NEPA by not assessing the environmental implications related to the Draft Guideline. The International Center for Technology Assessment supplemented the petition with a letter to Secretary Shalala, dated December 21, 1998, containing a large number of signatures in support of the petition.

After carefully reviewing the petition and related information, the request for the actions identified in 1 and 2 above has been denied. The remainder of this response discusses the reasons for denying these requests in relation to the major concerns identified in the petition. The response also identifies many of the considerations and actions DHHS has taken or intends to take that are relevant to the request to grant such other relief as the Secretary deems just and proper.

A. RESPONSE TO THE REQUEST TO INITIATE RULEMAKING TO PROHIBIT XENOTRANSPLANTATION

After carefully reviewing the petition, DHHS denies the request to initiate rulemaking proceedings to prohibit xenotransplantation. This section of the DHHS response discusses the rationale for this decision and addresses the major concerns expressed in the petition.

1. DHHS has maintained a continuous, open dialogue in the course of considering regulatory policies on xenotransplantation.

The petition alleges that DHHS failed to adequately consider the issues related to xenotransplantation by not giving sufficient consideration to infectious disease-related and other medical, social and ethical issues raised by xenotransplantation. On the contrary, DHHS has reviewed and continues to examine these issues in the course of developing its xenotransplantation policies. The Draft Guideline did not authorize the initiation of any xenotransplantation clinical trials; rather it provided general guidance to sponsors, investigators, and local review bodies involved in the development, conduct, and local approval of such trials with a view towards preventing and controlling diseases that may be transmitted by xenotransplantation.

DHHS believes that careful consideration of all relevant issues as well as public discourse on such issues are critical to the development of public policy. Development of the Draft Guideline is an excellent example of this. The Draft Guideline was developed over a two year period by staff from several DHHS components including the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), the National Institutes of Health (NIH), and the Office of the Assistant Secretary for Planning and Evaluation (OASPE). The United States Department of Agriculture (USDA) also provided expert input. In September 1996, the Draft Guideline was published in the Federal Register together with a request for public comment on the document. The more than 140 letters of comment received in response to the Draft Guideline addressed a broad array of issues, including clinical protocol responsibility, review and oversight, informed consent and patient education, xenotransplantation product sources, source animal screening and qualification, and biomedical archives and records. These comments, as well as recent scientific findings, are being carefully considered by DHHS in the crafting of the revised Guideline. Although this phase of public comment has concluded, DHHS welcomes further public input.

In development of xenotransplantation policies, DHHS has also sponsored or participated in numerous meetings on xenotransplantation. These activities are essential for both sharing information and receiving outside input on issues relevant to xenotransplantation. Attached is a list of examples of major meetings, both

domestic and international, that focused in whole or in part on xenotransplantation and were either sponsored by DHHS or included DHHS participants (see enclosure). DHHS will continue to promote open discussion of issues related to xenotransplantation. Consistent with this objective, DHHS is in the process of establishing the "Secretary's Advisory Committee on Xenotransplantation" (SACX), which will discuss ongoing and proposed protocols, consider the full range of complex scientific, medical, social, ethical, and public health concerns raised by xenotransplantation, and make recommendations to the Secretary on policy and procedures.

2. **DHHS has extensively considered and continues to consider the safety of xenotransplantation.**

The petition asserts that DHHS did not consider the potential safety risks of xenotransplantation in issuing the Draft Guideline. In fact, in developing the Draft Guideline to address public health issues raised by xenotransplantation, DHHS considered both the potential benefits as well as the potential risks posed by xenotransplantation. The Draft Guideline identified general principles for the prevention and control of infectious diseases that may be associated with xenotransplantation and that may pose a public health hazard. These principles addressed source animal selection (section 3), isolation of patients (section 4.3.1.2), pre- and post-transplant monitoring of patients (section 4.1), and informed consent and education (section 2.5).

However, the Draft Guideline is only one of several tools the DHHS has available to help assure the safe conduct of experimental xenotransplantation clinical investigations. There are additional, well established mechanisms for promoting safety in the clinical investigation of xenotransplantation. Under the Federal Food, Drug and Cosmetic Act (21 U.S.C. §321 et seq.) and the Public Health Service Act (42 U.S.C. §262), FDA has the authority to monitor and regulate xenotransplantation products, including investigational studies of such products. As stated at numerous public meetings and in the Draft Guideline (sec. 1, para. 2, page 49921), xenotransplantation products, like other investigational drugs or biological products, are subject to FDA regulations for investigational new drugs in 21 CFR Part 312. A sponsor who intends to conduct a clinical investigation of an experimental product must submit to FDA an Investigational New Drug Application (IND), which must include, among other things, adequate information to allow assessment of the risks of the proposed studies. An IND that does not contain sufficient information to assess risks or that poses an unreasonable and significant risk of illness or injury is subject to "clinical hold." 21 CFR §312.42. A clinical hold is an order issued by FDA to the

sponsor to delay or prohibit initiation of a proposed clinical investigation or to suspend an ongoing investigation.

The clinical study of an investigational new drug, including a xenotransplantation product, is also subject to other regulations. Consistent with 21 CFR Part 50, clinical investigators must inform study subjects about the potential risks, benefits, and objectives of the study and obtain their informed consent before enrolling the subjects into a study. In accordance with 21 CFR Part 56, an Institutional Review Board (IRB) must approve and continually monitor a clinical study. It is the responsibility of the IRB to safeguard the rights and welfare of human subjects. To approve a clinical study, IRBs must determine that risks to study subjects are minimized, that risks are reasonable when compared to the anticipated benefits, that selection of subjects is equitable, and that informed consent will be sought from prospective subjects and documented.

DHHS has previously taken, and will continue to take, action related to safety and public health issues raised by xenotransplantation. For example, in October 1997, FDA placed all clinical investigations of porcine xenotransplantation products on clinical hold until additional tests and scientific data could be developed to address safety concerns regarding porcine endogenous retrovirus. Such clinical trials have been allowed to proceed on a case-by-case basis once the safety concerns were adequately addressed. On April 6, 1999 (64 FR 16743), after review of the relevant science and consideration of public comments submitted in response to the Draft Guideline and expressed at public meetings, FDA announced the availability of "Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans." The term 'xenograft' used in the April 6, 1999 FDA Guidance for Industry document signifies products used for xenotransplantation, where xenotransplantation is defined as any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with nonhuman animal cells, tissues or organs. FDA, following consultation with other DHHS agencies, concluded that "the use of nonhuman primate xenografts in humans raises substantial public health safety concerns within the scientific community and among the general public; [that] current scientific data indicates that human subjects, including individual xenotransplant recipients, their close contacts, and the public at large, would be exposed to significant infectious disease risk by the use of nonhuman primate xenografts; and [that] further scientific research and evaluation is needed in order to obtain sufficient information to adequately assess and potentially to reduce the risks posed by nonhuman primate xenotransplantation." In the Guidance cited above, FDA stated that:

> "(1) an appropriate federal xenotransplantation advisory committee, such as a Secretary's Advisory Committee on Xenotransplantation (SACX),

currently under development within the DHHS, should address novel protocols and issues raised by the use of nonhuman primate xenografts, conduct discussions, including public discussions as appropriate, and make recommendations on the questions of whether and under what conditions the use of nonhuman primate xenografts would be appropriate in the United States.

(2) clinical protocols proposing the use of nonhuman primate xenografts should not be submitted to the FDA until sufficient scientific information exists addressing the risks posed by nonhuman primate xenotransplants. Consistent with FDA Investigational New Drug (IND) regulations [21 CFR 312.42(b)(1)(iv)], any protocol submission that does not adequately address these risks is subject to clinical hold (i.e., the clinical trial may not proceed) due to insufficient information to assess the risks and/or due to unreasonable risk.

(3) at the current time, FDA believes there is not sufficient information to assess the risks posed by nonhuman primate xenotransplantation. FDA believes that it will be necessary for there to be public discussion before these issues can be adequately addressed."

In suggesting that nonhuman animal sources are unsafe for transplantation or implantation into humans, the petition specifically mentions the use of imported nonhuman primates as sources for xenotransplantation products. The petition also charges that CDC has not provided species-specific regulations for nonhuman primates (NHP) in the Draft Guideline. The purpose of the Draft Guideline was to provide guidance, not promulgate regulations. CDC does, however, regulate the importation of animals, including NHP, that may pose a hazard to human or animal health through its Division of Quarantine. 42 CFR Part 71. Importers must register with CDC; certify that the imported NHP will be used only for scientific, educational, or exhibition purposes; implement disease control measures including quarantine, observation and health assessments; maintain records regarding each shipment; and report suspected zoonotic illness in animals or workers.

In addition, the United States Department of Agriculture, Animal and Plant Health Inspection Service, Veterinary Services (USDA/APHIS/VS), regulates the importation of all animals and animal-origin materials that could represent a disease risk to U.S. livestock. 9 CFR Part 122. Both importation and interstate transport of animals or animal-origin materials that may introduce or disseminate any contagious or infectious disease of animals require a USDA permit.

The U.S. Fish and Wildlife Service, within the Department of the Interior, also regulates the importation of certain live animals. The regulations in 5 CFR Part 10, et seq. implement the Endangered Species Act and the Convention on International Trade of Endangered Species by requiring import permits for specified animals, including certain nonhuman primates. These regulations also include humane handling provisions, some of which are designed to minimize disease risks. Similar permitting and handling requirements apply to the transportation and exportation of regulated animals.

In summary, DHHS believes that an adequate regulatory framework is in place to help assure the reasonable safety of the clinical investigation of xenotransplantation. As demonstrated by the clinical hold placed on clinical investigations of porcine xenotransplantation products, and as described in the FDA guidance document on NHP xenotransplantation products, DHHS has exercised and will continue to exercise its authority to prevent or halt clinical trials for safety reasons when warranted. DHHS will continue to examine, discuss, and when appropriate, further revise its policies regarding xenotransplantation. For the reasons discussed above, DHHS does not believe it is necessary to prohibit by regulation the clinical investigation of xenotransplantation.

3. DHHS considered the results of previous xenotransplantation studies in developing the Draft Guideline.

The petition alleges that DHHS did not consider the effectiveness of xenotransplantation before issuing the Draft Guideline and states that the history of xenotransplantation demonstrates its ineffectiveness. DHHS considered the previous history of xenotransplantation in developing the Draft Guideline. A failure to demonstrate efficacy to date for particular xenotransplantation products is not an adequate basis for prohibiting all future clinical study of xenotransplantation. Scientific advances, such as the development of recombinant DNA technologies and strategies for immunosuppression and for inducing immune tolerance, have increased the likelihood of developing clinically effective xenotransplant products. Scientific data derived from adequate and well controlled clinical trials could provide evidence of efficacy. Under FDA's IND regulations, clinical investigations of xenotransplantation in the U.S. are evaluated rigorously by FDA for adequacy of preclinical data, product manufacturing and safety, and clinical trial design. The investigational phase of drug development is intended to either demonstrate or refute the efficacy of a proposed therapeutic agent. Thus, while it is true that the efficacy of xenotransplantation is still uncertain, the same is true of any investigational drug regulated by FDA. Once clinical trials are completed, FDA reviews and determines, often with the input of an advisory committee of experts, whether the data obtained from clinical investigations support marketing approval.

The petition cites reports of studies involving patients who survived only one or more months following solid organ xenotransplantation as evidence of the lack of efficacy of xenotransplantation as an alternative to allotransplantation. However, if the intent of the transplant were to provide a bridge until a human organ could become available, this amount of time would be of clinical value.

In addition, the petition fails to consider certain xenotransplantation protocols, in which cellular transplantation has been studied in clinical trials under IND, that have provided preliminary evidence suggesting the possibility of clinical benefit. For example, published histological evidence documents survival of porcine neuronal cells and growth of nonhuman dopaminergic cells in the human brain following implantation of porcine neuronal cells as treatment for severe Parkinson's Disease (Deacon et al., Nature Med., 1997; Schumacher, et al., Nature Med., 1997). Although more research is needed, clinical improvement has been reported using the implantation of porcine neuronal cells for the treatment of patients with Parkinson's Disease or Huntington's Disease (Shumacher, et al., Amer. Assoc. Neurosurg., Proceedings of Congress of Neurological Sciences, 1998; St. Hillaire, et al., Neurology, 1998). Thus, contrary to the statements in the petition, there is evidence to support further investigation of xenotransplantation. It is the intention of DHHS to provide guidance and a framework for monitoring such research to allow it to be performed in a safe and prudent manner.

4. **The Public Health Service Act does not require the Administrator of the Agency for Health Care Policy and Research (AHCPR) to conduct assessments of any specific health care technology.**

The petition asserts that DHHS did not adequately consider the cost of xenotransplantation in issuing the Draft Guideline. The petition also states that DHHS acted arbitrarily and capriciously in issuing the Draft Guideline because xenotransplantation is not a cost effective technology. It is not a foregone conclusion that xenotransplantation would increase health care costs. Well designed and carefully conducted preclinical studies and clinical trials are needed to evaluate the safety and efficacy of xenotransplantation products in treating particular diseases. For example, it is possible that products that utilize small numbers of cells, especially those obtained from established cell lines of animal origin (e.g., pancreatic islet cells or neuronal cells), could result in a significant reduction in the overall financial impact of certain illnesses (e.g., diabetes mellitus or Parkinson's Disease, respectively). Furthermore, even if a particular type of xenotransplantation product proves to be a safe and effective but costly therapeutic modality, the development and application of many common life-saving medical technologies in use today have been or are costly.

Magnetic resonance imaging, autologous or allogeneic bone marrow transplantation, and solid organ transplantation are examples.

The petition further asserts that DHHS failed to consider certain factors when assessing health care technology, in violation of the Public Health Service Act, 42 U.S.C. §299a-2(b). This provision authorizes the Administrator of the AHCPR, an agency of the Public Health Service, to conduct and support specific assessments of health care technologies and, in doing so, to consider certain factors such as the safety, efficacy, and effectiveness of the technologies and cost effectiveness "where cost information is available and reliable."

Technology assessments conducted by AHCPR or supported under contracts involve a methodologically rigorous review and abstraction of published literature, followed by critical evaluation and synthesis of the evidence with respect to the particular technology. When a technology is under development and the pertinent scientific literature is sparse or not available at all, for example, with respect to its safety and efficacy, an assessment based on published research would be premature. As noted above, section 299a-2(b)(2) does not require that the cost effectiveness of health care technologies be considered when there is a lack of reliable information pertaining to costs, a situation that is common when procedures are in the experimental stage.

42 U.S.C. §299a-2 does not require the Administrator of AHCPR to conduct an assessment of xenotransplantation or of any other specific health care technology. Rather, the statutory construct of section 299a-2, in subsections (c)(1), (d)(4), and (e), recognizes that AHCPR assessments must be prioritized. To rise to the level of a priority assessment, either the Administrator receives a request under paragraph (d) from the Secretary, the Health Care Financing Administration (HCFA), or the Department of Defense that AHCPR conduct or support an assessment, or the Administrator may elect, pursuant to subsection (d)(3) or (f), to undertake an assessment at his or her own initiative. Normally, such an election would be stimulated by one or more requests from outside the agency supporting the importance of the assessment or as a result of the Administrator's consultation with the National Advisory Council for Health Care Policy, Research, and Evaluation (established by 42 U.S.C. 299c) regarding the establishment of an annual list of assessments, in accordance with subsection (c) of the statute

Thus, there is no basis for the petitioners' claim that the Public Health Service Act requires the Administrator of AHCPR to conduct assessments of any aspect of xenotransplantation.

5. **DHHS has considered and continues to consider the social, legal, and ethical issues of xenotransplantation.**

The petition asserts that DHHS did not adequately consider the social, legal, and ethical implications of xenotransplantation before issuing the Draft Guideline. DHHS has always recognized that xenotransplantation raises complex social, legal, and ethical issues that merit ongoing public discourse. However, these issues are beyond the scope of the Draft Guideline, which was developed to address primarily the infectious disease issues associated with xenotransplantation. Public discussion is an effective means of gathering and exchanging a broad range of views on xenotransplantation. Consequently, and as discussed previously in this response, DHHS has organized and/or participated in a number of meetings and workshops at which these issues were addressed. In addition, DHHS is in the process of establishing the SACX, which will provide a forum for public discussion of and input on xenotransplantation issues.

6. **DHHS has considered multiple approaches to alleviate the shortage of human organs for clinical transplantation.**

The petition asserts that the United States Government and medical communities have not acted to alleviate the shortage of human organs for transplantation. Independent of the question of whether any xenotransplantation procedures will ultimately be shown to be safe and effective, DHHS recognizes that there is a need for increasing the availability of human organs for transplantation and has taken an active role in addressing this issue. A few examples are discussed below.

On 12/15/97, the Clinton Administration launched the National Organ and Tissue Donation Initiative (http://www.hhs.gov/news/press/1997.html). This initiative created a broad national partnership of public, private, and volunteer organizations that have joined in an effort to increase awareness about organ and tissue donation and to increase the public's willingness to donate. HRSA and other DHHS agencies and offices are working with dozens of organizations such as the American Bar Association, the National Conference of State Legislatures, the Home Depot, the Coalition on Donation, Kaiser Permanente, the University of Rhode Island, Saturn Corporation, and the Congress of National Black Churches to increase the currently low rates of family consent to donation. DHHS partnered with the Coalition on Donation to use its national message "Share your life. Share your decision." and to establish a toll-free number for individuals to obtain a brochure on organ donation. DHHS also partnered with major national faith organizations and the transplant community in support of National Donor Sabbath to facilitate these organizations' efforts to encourage donation among members of their congregations. Through the National Initiative, DHHS created an internet site titled "Organ Donation" at http://www.organdonor.gov/ that provides information on organ and tissue donation. These are only a few of the activities accomplished through the Initiative. Others are

noted in the National Initiative's Management Plan accessible on the aforementioned web site.

As part of the National Initiative, HCFA recently published a final rule on conditions of hospital participation amending 42 CFR Part 482 ([63 FR 33856, June 22, 1998], Medicare and Medicaid Programs; Hospital Conditions of Participation; Identification of Potential Organ, Tissue, and Eye Donors and Transplant Hospitals' Provision of Transplant-Related Data). This rule requires hospitals to refer all deaths or imminent deaths to organ procurement organizations (OPO). Based on results seen in states with similar laws and provisions, this rule is expected to have a substantial impact on donation. The rule also requires adequate training of hospital-based requester. DHHS has committed resources to OPOs and hospitals to assist them in implementation of this regulation and, in June 1998, HCFA and HRSA jointly sponsored a two-day workshop attended by OPO representatives, hospital administrators, representatives of national associations, donor families, physicians, and researchers with the goal of developing a resource guide for training and educating designated requester and other professionals involved in the donation process.

HRSA provides funding and oversight for the nation's Organ Procurement and Transplantation Network (OPTN). The contractor is required to perform several tasks related to public and professional education to increase requests and consent for organ donation. For example, the contractor must: (1) conduct and evaluate educational activities for health care professionals (particularly those who procure organs for transplantation), (2) develop a plan to utilize health care professionals, donor family members, and transplant recipients in the OPTN's educational activities, (3) serve as a national resource to transplant and health professionals, as well as the general public, for information concerning donation and transplantation, (4) establish liaisons with national level groups responsible for licensing and certifying various health professionals, and encourage transplant-related items in board and certifying exams, and (5) provide a toll-free telephone number through which the public can obtain information on organ donation. The contractor must also coordinate the National Exhibit Consortium, which consists of a number of transplant organizations that contribute funds to provide a display at various large group meetings of health professionals and the general public to increase awareness about organ donation.

Another approach being pursued by DHHS is to determine effective methods to increase human organ and tissue donation. HRSA launched a $5 million grant program in 1999 to explore promising interventions for increasing donation, especially by increasing consent rates when the request for donation is made. The effectiveness of these proposed interventions will be determined using rigorous evaluation methods incorporated into the study.

HRSA has sponsored a series of Institute of Medicine (IOM) studies to investigate

non-heart-beating donors (NHBD) as an alternative organ donor source. The IOM is working with OPOs and transplant programs to develop recommendations on NHBD protocol development, determination of death, and donor family issues. In May 1999, the IOM held a conference to reach consensus, thereby facilitating broader acceptance in the OPO community of NHBD and non-heart-beating donor protocols. Recommendations will be shared with the transplant community in the near future.

A. RESPONSE TO THE REQUEST THAT DHHS ISSUE AN ENVIRONMENTAL ASSESSMENT (EA) OR AN ENVIRONMENTAL IMPACT STATEMENT (EIS) IN ACCORDANCE WITH THE NATIONAL ENVIRONMENTAL POLICY ACT (NEPA).

The issuance of the Draft Guideline is not a "major federal action" under the National Environmental Policy Act, and therefore, the Department is not required, under NEPA, to prepare an environmental assessment or an environmental impact statement for the Draft Guideline.

The petition alleges that DHHS issuance of the Draft Guideline is a major federal action significantly affecting the quality of the human environment. It further alleges that DHHS failed to comply with the requirements of NEPA because DHHS did not prepare an environmental assessment or an EIS before issuing the Draft Guideline.

Under Council on Environmental Quality (CEQ) regulations, which are given deference by the courts (*see Andrus v. Sierra Club*, 442 U.S. 347, 358 (1979)), a "major federal action" includes actions which are "potentially subject to Federal control and responsibility." 40 CFR §1508.18. The Draft Guideline discusses general principles for the prevention and control of infectious diseases that may be associated with xenotransplantation. DHHS, through issuance of this Guideline in either draft or revised form, is not asserting federal control and responsibility over xenotransplantation research nor establishing any requirements that researchers must follow in the conduct of xenotransplantation research. Thus, the issuance of the Guideline is not a major federal action under NEPA, and therefore the Department is not required, under NEPA, to prepare an environmental assessment or an environmental impact statement for the Draft guideline or for any revised Guideline that may follow. *See Wyoming Outdoor Council v. United States Forest Serv.*, 165 F.3d 43, 49 (D.C.Cir. 1999) ("(T)he law does not require an agency to prepare an EIS until it reaches the critical stage of a decision which will result in 'irreversible and irretrievable commitment of resources' to an action that will affect the environment." (quoting Mobil Oil Corp. v. FTC, 562 F.2d 170, 173 (2d Cir. 1977).

The petition also alleges that DHHS failed to consider alternatives to xenotransplantation, as required by NEPA. Because the Draft Guideline is not a "major federal action" under NEPA, for the reasons discussed above, DHHS does not have to conduct an environmental review under NEPA, which review would otherwise include a discussion of alternatives including the proposed action. 40 CFR §1502.14.

E. SUMMARY

1. **The request that DHHS initiate rulemaking to prohibit xenotransplantation is denied.**

   As described above, DHHS has taken, and will continue to take appropriate action to ensure a reasonable and cautious approach toward the investigation of xenotransplantation. At present, DHHS does not believe that currently available information warrants rulemaking to categorically prohibit xenotransplantation. As the science related to xenotransplantation evolves, however, DHHS will continue to review its policies and revise them as necessary.

2. **The request to issue an environmental assessment or an environmental impact statement under the National Environmental Policy Act is denied.**

   As discussed above, neither the issuance of the Draft Guideline nor the publication of a revised Guideline is a "major federal action" under NEPA. Therefore, DHHS is not conducting an environmental review for the Guideline (in either draft or revised form). To the extent that DHHS or any of its agencies engages in xenotransplantation activities that are major federal actions under NEPA, DHHS and its agencies will comply with the requirements of NEPA.

   DHHS encourages public interest and participation in the development of public health policies related to xenotransplantation. Please be assured that DHHS will continue to carefully consider all views to assure that reasonable and prudent policies are developed.

Sincerely yours,

David Satcher, M.D., Ph.D.
Assistant Secretary for Health
and Surgeon General

Enclosures

GLOSSARY OF ABBREVIATIONS

AHCPR	Agency for Health Care Policy and Research
AIDS	Acquired Immunodeficiency Syndrome
APHIS	Animal and Plant Health Inspection Service
BRMAC	Biological Response Modifiers Advisory Committee (FDA advisory committee)
CDC	Centers for Disease Control and Prevention
CEQ	Council on Environmental Quality
CFR	Code of Federal Regulations
DHHS	Department of Health and Human Services
EA	Environmental Assessment
EIS	Environmental Impact Statement
FDA	Food and Drug Administration
FOI	Freedom of Information
FR	Federal Register
HCFA	Health Care Financing Administration
HICPAC	Hospital Infection Control Practices Advisory Committee (CDC advisory committee)
ICAAC	Interscience Conference on Antimicrobial Agents and Chemotherapy
IND	Investigational New Drug Application
IOM	Institute of Medicine
IRB	Institutional Review Board
HRSA	Health Resources and Services Administration
NEPA	National Environmental Protection Act
NIH	National Institutes of Health
NHBD	Non-heart-beating donors
NHP	Nonhuman Primate(s)
OASPE	Office of the Assistant Secretary for Planning and Evaluation
OECD	Organization for Economic Cooperation and Development
OPO	Organ Procurement Organization
OPTN	Organ Procurement and Transplantation Network
PHS	Public Health Service
PRIM&R	Public Responsibility in Medicine and Research
SACX	Secretary's Advisory Committee on Xenotransplantation
UKXIRA	United Kingdom Xenotransplantation Interim Regulatory Authority
USC	United States Code
USDA	United States Department of Agriculture
VS	Veterinary Services
WHO	World Health Organization

REFERENCES

DHHS:

"Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation." 61 FR, 49920-49932, September 23, 1996.

FDA:

"Guidance for Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans. Notice of availability," 64 FR 16743-16744, April 6, 1999. The document can be found on the internet at http://www.fda.gov/cber/gdlns/xenoprim.txt (.txt file) or http://www.fda.gov/cber/gdlns/xenoprim.pdf (.pdf file).

Copies of FDA advisory committee transcripts can be obtained by writing to:

The Freedom of Information Office (HFI-35)
5600 Fisher's Lane
Rockville, MD 20857.

Further information on how to submit an FOI request can be obtained by fax (301) 443-1726 or phone (301) 827-2000.

Recent FDA advisory committee transcripts are also available at http://www.fda.gov/ohrms/dockets/ac/acmenu.htm

Health Canada:

"Report of the National Forum on Xenotransplantation; Clinical, Ethical and Regulatory Issues," Therapeutic Products Programme, Health Canada, November 6-8, 1997

"Proposed Canadian Standard for Xenotransplantation," available at http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/btox.html#standards.

World Health Organization (WHO):

Report of WHO Consultation on Xenotransplantation. Geneva, Switzerland, 28-30 October 1997. Sponsored by the World Health Organization. (Document WHO/EMC/ZOO/98.1: available from Division of Emerging and Other Communicable Disease Surveillance and Control, WHO, 1211 Geneva 27, Switzerland.)

Referenced Scientific Publications:

Deacon, T. et al., "Histological Evidence of fetal pig neural cell survival after transplantation into a patient with Parkinson's Disease," *Nature Med.* 3:350-353, 1997

Schumacher, J.M. et al., "Neurohal xenotransplantation in Parkinson's Disease," *Nature Med.*, 3:474-475, 1997

Schumacher, J.M. et al.; "Transplantation of fetal pig cells for Parkinson's disease: preliminary results," *Amer. Assoc. Neurosurg.*, Proceedings of Congress of Neurological Sciences, April, 1998, p. 156-157

St. Hillaire, M. et al., "Transplantation of fetal porcine striatal cells in Huntington's disease: preliminary safety and efficacy results," *Neurology* 50 (suppl. 4), 1998, abstract S10.008

Other Publications:

Xenotransplantation. Scientific Frontiers and Public Policy. Fishman, J., Sachs, D., Shaikh, R. (eds.), *Ann. N. Y. Acad .Sci.*, vol. 862, 1998

The DHHS Interagency Working Group on Xenotransplantation, The Draft U.S. Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation, *Ann. N. Y. Acad. Sci.* vol. 862:166, 1998.

Chapman, L.E. et al., "Xenotransplantation and Xenogeneic Infections," *New Eng. J. Med.*, 333:1498, 1995

Daar AS. Animal-to-human organ transplants. Round table discussion: JS Allan, APR Aluwihare, FH Bach, A Caplan, L Chapman, BM Dickens, JA Fishman, CG Groth, and ME Breimer, A Menache, PJ Morris, E Van Rongen. *Bulletin of the World Health Organization* 1999: 77:54-81.

MEETINGS

Major Meetings Addressing Xenotransplantation in which DHHS Has Been Involved

11/94: Institute of Medicine (IOM) Drug Forum: FDA presented safety concerns regarding proposed transplantation of porcine cells to humans

12/94: FDA's Biological Response Modifiers Advisory Committee (BRMAC): discussed concerns raised by xenogeneic tissues intended for transplantation

4/95: FDA's BRMAC considered xenogeneic infectious disease concerns and an IND submitted to FDA for the use of porcine cellular transplants

5/95: American Society of Transplant Surgeons. Chicago, Illinois, Symposium on Public Health Concerns in Xenotransplantation

6/95: IOM Xenotransplantation Workshop [Published report: "Xenotransplantation: Science, Ethics, and Public Policy. Washington, D.C., National Academy Press, 1996]

7/95: FDA's BRMAC considered proposed xenotransplantation protocols for treatment of an AIDS patient

1/96: Fourth National Symposium on Biosafety: Working Safely with Research Animals, Atlanta Georgia. Plenary Symposium on Public Health Issues in Xenotransplantation [Proceedings available on internet: http://www.cdc.gov/od/ohs/symposium_idx.htm#contents]

3/96: Animal Care and Use: Hot Zones, Grey Zones and "Go Slow " Zones. Conference, Boston, MA, March 15, 1996 [Proceedings available from Public Responsibility in Medicine and Research (PRIM&R), 132 Boylston Street, Boston, MA 02116, 617-423-4112]

5/96: American Society of Transplant Physicians, Plenary Symposium on Xenotransplantation. Dallas, Texas

11/96 Strategies for Addressing the IRB's Current Obstacles: Holding it Together and Measuring Our Success, November 11-12, 1996, San Diego, CA. Session on xenotransplantation [Proceedings available from PRIM&R, 132 Boylston Street, Boston, MA 02116, 617-423-4112]

11/96: National Kidney Foundation, Symposium on Xenotransplantation and Public Health. New Orleans, Louisiana

11/96: American Public Health Association. Symposium on Xenotransplantation and Public Health

12/96: CDC's Hospital Infection Control Practices Advisory Committee (HICPAC): discussion of the Draft Guideline (12/12-13/96)

3/97: Prevention '97. Symposium on Emerging Infectious Diseases featured invited presentation on public health concerns in xenotransplantation, Atlanta, Georgia

7/97: First PHS Xenotransplantation Workshop: Cross species infectivity and pathogenesis [Available on the internet at http://www.niaid.nih.gov/dait/cross-species/default.htm]

9/97: Balancing Xenomania and Xenophobia. Social and Ethical Issues in Xenotransplantation at Ohio State University Medical Center, Columbus, Ohio

9/97: Fourth International Xenotransplantation Conference, Nantes, France

10/97: WHO Consultation on Xenotransplantation, Geneva, 28-30 October, 1997 ["Report of WHO Consultation on Xenotransplantation, Geneva, Switzerland, 28-30 October, 1997" (document WHO/EMC/ZOO/98.2) and "Xenotransplantation: Guidance on infectious disease prevention and management" (document WHO/EMS/ZOO/98), both available from Division of Emerging and Other Communicable Diseases Surveillance and Control, WHO, 1211 Geneva 27, Switzerland]

11/97: Canadian National Forum on Xenotransplantation [see Proposed Canadian Standard for Xenotransplantation. Available on the internet at http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/btox.html#standards.]

12/97: Xenotransplantation Subcommittee of FDA's BRMAC: considered public health issues concerning cross-species transplantation [Available on the internet at http://www.fda.gov/ohrms/dockets/ac/cber97t.htm]

1/98: Second PHS Xenotransplantation Workshop: Developing Public Health Service Policy in Xenotransplantation [Available on the internet at http://www.fda.gov/ohrms/dockets/dockets/96m0311/96m0311.htm]

3/98: "International issues in transplantation biotechnology, including the use of non-human cells, tissues and organs." [Report of meeting: Xenotransplantation: International Policy Issues, Organization for Economic Cooperation and Development Proceedings prepared by Elettra Ronchi, OECD Secretariat, OECD Publications, Paris, France, 1999; and Proceedings published: Xenotransplantation: Scientific Frontiers and Public Policy. Proceedings of an OECD/New York Academy of Sciences Workshop on Xenotransplantation. Edited by J Fishman, D Sachs, and R Shaikh. Annals of the New York Academy of Science 1998; volume 862]

4/98: Transplant Infectious Disease World Congress. Symposium on Xenotransplantatio Orlando, Florida

5/98: American Society for Microbiology 98th General Meeting. Plenary Symposium o emerging infections featured invited talk on xenotransplantation

7/98: The Transplantation Society XVII World Congress. Plenary Symposium and multi sections on xenotransplantation, Montreal, Canada [Proceedings published in Transplant. Proceedings, volume 31, 1999]

8/98: The United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA sponsored a workshop on Porcine Endogenous Retroviruses

9/98: The 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICA Plenary Symposium on Emerging Infectious Public Health Issues included invited talk on xenotransplantation [Published as: "Infectious Disease Issues in Xenotransplantation. Cha Emerging Infections 3, E. Michael Scheld, William A. Craig, James M. Hughes, Eds., Am Society of Microbiology Press, Washington DC, 1999, pp. 165-179]

10/98: American Society for Nephrology. Symposium on Xenotransplantation. Philadelph Pennsylvania

2/99: Ethical and Legal Aspects of Xenotransplantation. Sponsored by Sonderforschungsb 265, Hannover Medical School, at Evangelische Akademie Loccum, Germany, February 1 1999

3/99: Seminar on microbiological hazards related to xenotransplantation, The Swedish Committee on Xenotransplantation, Almare Stäkets Herrgård, Stockholm, Sweden, March 1999

4/99: Experimental Biology '99. Symposium on xenotransplantation, Washington DC [Proceedings to be published in Clinical and Experimental Pharmacology and Physiology i 1999]

5/99: Xenotransplantation: A Scientific Basis for Risk Assessment. The Banbury Center, C Spring Harbor Laboratory, New York, May 9-12, 1999

6/99: Xenotransplantation Subcommittee of FDA's BRMAC: considered new data and publ health issues concerning cross-species transplantation [Available on the internet at http://www.fda.gov/ohrms/dockets/ac/99mtbc.htm]

7/99: The United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) workshop on xenotransplantation surveillance