Supporting Statement for
Infectious Disease Issues in Xenotransplantation
0910-0456

A. JUSTIFICATION

1. Need and Legal Basis

The Food and Drug Administration (FDA) is requesting an extension of Office of Management and Budget (OMB) Control No. 0910-0456 and OMB approval of the information collection provisions contained in a document entitled “PHS Guideline on Infectious Disease Issues in Xenotransplantation” (PHS Guideline) (Tab A). The information provisions are listed below:

Table 1-Reporting Recommendations	
Section of PHS Guideline	Description
3.2.7.2	Notify sponsor or FDA of new archive site when source animal facility or sponsor ceases operations.
3.4	Standard operation procedures (SOPs) of source animal facility should be available to review bodies.
3.5.1	Include increased infectious risk in informed consent if source animal quarantine period of 3 weeks is shortened.
3.5.4	Sponsor to make linked records described in section 3.2.7 available for review.
3.5.5	Source animal facility to notify clinical center when infectious agent is identified in source animal or herd after xenotransplantation product procurement.

Table 2-Recordkeeping Recommendations	
Section of PHS Guideline	Description
3.2.7	Establish records linking each xenotransplantation product recipient with relevant records.
4.3	Sponsor to maintain cross-referenced system that links all relevant records (recipient, product, source animal, animal procurement center, and significant nosocomial exposures).

3.4.2	Document results of monitoring program used to detect introduction of infectious agents that may not be apparent clinically.
3.4.3.2	Document full necropsy investigations including evaluation for infectious etiologies.
3.5.1	Justify shortening a source animal's quarantine period of 3 weeks prior to xenotransplantation product procurement.
3.5.2	Document absence of infectious agent in xenotransplantation product if its presence elsewhere in source animal does not preclude using it.
3.5.4	Add summary of individual source animal record to permanent medical record of the xenotransplantation product recipient.
3.6.4	Document complete necropsy results on source animals (50 year record retention).
3.7	Link xenotransplantation product recipients to individual source animal records and archived biologic specimens.
4.2.3.2	Record base-line sera of xenotransplantation health care workers and specific nosocomial exposure.
4.2.3.3 and 4.3.2	Keep a log of health care workers' significant nosocomial exposure(s).
4.3.1	Document each xenotransplant procedure.
5.2	Document location and nature of archived PHS specimens in health care records of xenotransplantation product recipient and source animal.

The statutory authority to collect this information is provided under sections 351 and 361 of the Public Health Service Act (PHS Act, 42 U.S.C. 262 and 264)(Tab B) and the provisions of the Federal, Food, Drug, and Cosmetic Act (the Act) that apply to drugs (21 U.S.C. 301 et seq.).

In 2001, the FDA on behalf of PHS announced the PHS Guideline (see Tab A) to address the infectious disease concerns raised by xenotransplantation. The PHS guideline was jointly developed by agencies within the PHS of the Department of Health and Human Services (DHHS) -- FDA, the Centers for Disease Control and Prevention, the Health Resources and Services Administration, the National Institutes of Health, as well as the DHHS Office of the Assistant Secretary for Planning and Evaluation. The PHS guideline is intended to protect the public health and help ensure the safety of using xenotransplantation products in

humans by preventing the introduction, transmission, and spread of infectious diseases associated with xenotransplantation.

2. Information Users

The PHS guideline recommends procedures to diminish the risk of transmission of infectious agents to the xenotransplantation product recipient and the general public. The PHS guideline is intended to address public health issues raised by xenotransplantation, through identification of general principles of prevention and control of infectious diseases associated with xenotransplantation that may pose a hazard to the public health. The collection of information described in this PHS guideline is intended to provide general guidance to sponsors in: (1) The development of xenotransplantation clinical protocols, (2) the preparation of submissions to FDA, and (3) the conduct of xenotransplantation clinical trials. Also, the collection of information will help ensure that the sponsor maintains important information in a cross-referenced system that links the relevant records of the xenotransplantation product recipient, xenotransplantation product, source animal(s), animal procurement center, and significant nosocomial exposures. The PHS guideline describes an occupational health service program for the protection of health care workers involved in xenotransplantation procedures, caring for xenotransplantation product recipients, and performing associated laboratory testing. The PHS guideline also describes a public health need for a national xenotransplant database which is currently under development by the PHS.

3. Improved Information Technology

Sponsors may use computerized storage e.g., (tapes, discs, CD-Rom’s), microfiche or microfilm to record and store data and information rather than hard copy records if they choose. Notification can be made by phone, fax, or mail. We are not aware of any other improved technology to reduce the burden.

4. Duplication of Similar Information

PHS is the only agency that recommends collecting this information. This information is not available from any other source.

5. Small Businesses

Although FDA must apply the statutory and regulatory

requirements equally among all enterprises, FDA does provide special help to small businesses. CBER's Office of Communication, Training and Manufacturers Assistance, provides assistance to small businesses subject to FDA's regulatory requirements.

6. Less Frequent Collection

The recommendations provided in the PHS guideline are intended to diminish the risk of transmission of infectious agents to the xenotransplantation product recipient and to the general public. Less frequent collection of information would not provide the necessary information needed to help prevent the transmission of infectious agents to xenotransplantation products recipients and the general public.

There are no technical or legal obstacles to reducing the burden.

7. Special Circumstances

A sponsor may be required to submit to FDA proprietary trade secret or other confidential information when providing requested information. FDA has instituted security measures to protect confidential information received from manufacturers and will, to the extent permitted by law, protect this information.

Because xenotransplantation is a relatively new area of medical science, potential problems and adverse effects are not well known. Because of the potential risk for cross-species transmission of pathogenic persistent virus, the guideline recommends that health records be retained for 50 years. Since these records are medical records, the retention of such records for up to 50 years is not information subject to the PRA (5 CFR 1320.3(h)(5)). Also, because of the limited number of clinical studies with small patient populations, the number of records is expected to be insignificant at this time. The retention period is intended to assist health care practitioners and officials in surveillance and in tracking the source of an infection, disease, or illness that might emerge in the recipient, the source animal, or the animal herd or colony after a xenotransplantation.

8. *FederalRegister* Notice/Outside Consultation

In accordance with 5 CFR 1320.8(d), on June 22, 2006, in Volume 71, No. 120, page 35911, a 60-day notice for public comment (Tab

C) was published in the FEDERAL REGISTER. No comments were received from the public.

9.Payment/Gift to Respondent

FDA has not provided and has no intention to provide any payment or gift to respondents.

10. Confidentiality

The confidentiality of information received by FDA would be consistent with the Freedom of Information Act and the agency's regulations under 21 CFR part 20. Proprietary or trade secret information is deleted from any information released by FDA under the Freedom of Information Act and FDA regulations.

11. Sensitive Questions

Questions of a sensitive nature are not applicable to this information collection.

12. Burden Estimate (Total Hours and Wages)

The total annual estimated burden for this collection of information is 155.76 hours.

Table 3-Estimated Annual Reporting Burden

PHS Guideline Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
3.2.7.2[1]	1	1	1	0.5	0.50
3.4[2]	12	0.33	4	0.08	0.32
3.5.1[3]	12	0.08	(0-1) 1	0.25	0.25
3.5.4[4]	12	1	12	0.5	6.0
3.5.5[3]	18	0.06	(0-1) 1	0.2	0.2
Total					7.27

[1] No animal facility or sponsor has ceased operations in the last 3 years; however, we are using 1 respondent for estimation purposes.
[2] FDA's records indicate that an average of 4 INDs are expected to be submitted per year.
[3] To our knowledge, has not occurred in the past 3 years and is expected to continue to be a rare occurrence.
[4] Based on an estimate of 36 patients treated over a 3 year period, the average number of xenotransplantation product recipients per year is estimated to be 12.

Table 4-Estimated Annual Recordkeeping Burden					
PHS Guideline Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
3.2.7[1]	1	1	1	16	16.0
4.3[2]	12	1	12	0.83	9.96
3.4.2[3]	12	11	132	0.25	33.0
3.4.3.2[4]	18	4	72	0.3	21.6
3.5.1[5]	12	0.08	(0-1) 1	0.5	0.5
3.5.2[5]	12	0.08	(0-1) 1	0.25	0.25
3.5.4	12	1	12	0.17	2.04
3.6.4[6]	12	2	24	0.25	6.0
3.7[6]	18	1.33	24	0.08	1.92
4.2.3.2[7]	12	25	300	0.17	51.0
4.2.3.2[5]	12	0.08	(0-1) 1	0.17	0.17
4.2.3.3 and 4.3.2[5]	12	0.08	(0-1) 1	0.17	0.17
4.3.1	12	1	12	0.25	3.0
5.2[8]	12	3	36	0.08	2.88
Total					148.49

[1]A one-time burden for new respondents to set up a recordkeeping system linking all relevant records. FDA estimates 1 new sponsor annually.
[2]FDA estimates there is minimal recordkeeping burden associated with maintaining the record system.
[3]Monitoring for sentinel animals (subset representative of herd) plus all source animals. There are approximately 6 sentinel animals per herd x 1 herd per facility x 18 facilities = 108 sentinel animals. There are approximately 24 source animals per year (see footnote 6 of this table); 108 + 24 = 132 monitoring records to document.
[4]Necropsy for animal deaths of unknown cause estimated to be approximately 4 per herd per year x 1 herd per facility x 18 facilities = 72.
[5]Has not occurred in the past 3 years and is expected to continue to be a rare occurrence.
[6]On average 2 source animals are used for preparing xenotransplantation product material for one recipient. The average number of source animals is 2 source animals per recipient x 12 recipients annually = 24 source animals per year. (See footnote 4 of table 3 of this document)
[7]FDA estimates there are approximately 12 clinical centers doing xenotransplantation procedures x approximately 25 health care workers involved per center = 300 health care workers.
[8]24 source animal records + 12 recipient records = 36 total records.

Respondents to this collection of information are the sponsors of clinical studies of investigational xenotransplantation products under investigational new drug applications (INDs) and xenotransplantation product procurement centers, referred to as source animal facilities. There are an estimated 12 respondents who are sponsors of INDs that include protocols for xenotransplantation in humans. Other respondents for this collection of information are an estimated 18 source animal

facilities which provide source xenotransplantation product material to sponsors for use in human xenotransplantation procedures. These 18 source animal facilities keep medical records of the herds/colonies as well as the medical records of the individual source animal(s). The total annual reporting and recordkeeping burden is estimated to be approximately 156 hours. The burden estimates are based on FDA's records of xenotransplantation-related INDs and estimates of time required to complete the various reporting and recordkeeping tasks described in the guideline. FDA does not expect the level of clinical studies using xenotransplantation to increase significantly in the next few years.

Information collections in this guideline not included in tables 1 through 4 can be found under existing regulations and approved under the OMB control numbers as follow: (1) “Current Good Manufacturing Practice for Finished Pharmaceuticals,” 21 CFR 211.1 through 211.208, approved through 9/30/2008 under OMB control number 0910-0139; (2) “Investigational New Drug Application,” 21 CFR 312.1 through 312.160, approved through 5/31/2009 under OMB control number 0910-0014; and information included in a license application, 21 CFR 601.2, approved through 9/30/2008 under OMB control number 0910-0338. (Although it is possible that a xenotransplantation product may not be regulated as a biological product (e.g., it may be regulated as a medical device), FDA believes, based on its knowledge and experience with xenotransplantation, that any xenotransplantation product subject to FDA regulation within the next 3 years will most likely be regulated as a biological product.) However, FDA recognized that some of the information collections go beyond approved collections; assessments for these burdens are included in tables 1 through 4.

In table 5 of this document, FDA identifies those information collection activities that are already encompassed by existing regulations or are consistent with voluntary standards which reflect industry’s usual and customary business practices.

Table 5-Collection of Information Required by Current Regulations and Standards

PHS Guideline Section	Description of Collection of Information Activity	21 CFR Section (unless otherwise stated)
2.2.1	Document off-site collaborations	312.52
2.5	Sponsor ensure counseling patient + family + contacts	312.62(c)
3.1.1 and	Document well-characterized health	312.23(a)(7)(a)

3.1.6	history and lineage of source animals	and 211.84
3.1.8	Registration with and import permit from the Centers for Disease Control and Prevention	42 CFR 71.53
3.2.2	Document collaboration with accredited microbiology labs	312.52
3.2.3	Procedures to ensure the humane care of animals	9 CFR parts 1, 2, and 3 and PHS Policy[1]
3.2.4	Procedures consistent for accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) and consistent with the National Research Council's (NRC) Guide	AAALAC International Rules of Accreditation[2] and NRC Guide[3]
3.2.5, 3.4, and 3.4.1	Herd health maintenance and surveillance to be documented, available, and in accordance with documented procedures; record standard veterinary care	211.100 and 211.122
3.2.6	Animal facility SOPs	PHS Policy[1]
3.3.3	Validate assay methods	211.160(a)
3.6.1	Procurement and processing of xenografts using documented aseptic conditions	211.100 and 211.122
3.6.2	Develop, implement, and enforce SOPs for procurement and screening processes	211.84(d) and 211.122(c)
3.6.4	Communicate to FDA animal necropsy findings pertinent to health of recipient	312.32(c)
3.7.1	PHS specimens to be linked to health records; provide to FDA justification for types of tissues, cells, and plasma, and quantities of plasma and leukocytes collected	312.23(a)(6)
4.1.1	Surveillance of xenotransplant recipient; sponsor ensures documentation of surveillance program life-long (justify >2 yrs.); investigator case histories (2 yrs. after investigation is discontinued)	312.23(a)(6)(iii)(f) and (g), and 312.62(b) and (c)

4.1.2	Sponsor to justify amount and type of reserve samples	211.122
4.1.2.2	System for prompt retrieval of PHS specimens and linkage to medical records (recipient and source animal)	312.57(a)
4.1.2.3	Notify FDA of a clinical episode potentially representing a xenogeneic infection	312.32
4.2.2.1	Document collaborations (transfer of obligation)	312.52
4.2.3.1	Develop educational materials (sponsor provides investigators with information needed to conduct investigation properly)	312.50
4.3	Sponsor to keep records of receipt, shipment, and disposition of investigative drug; investigator to keep records of case histories	312.57 and 312.62(b)

[1]The "Public Health Service Policy on Humane Care and Use of Laboratory Animals" (http://www.grants.nih.gov/grants/olaw/references/phspol.htm).
[2]AAALAC International Rules of Accreditation (http://www.aaalac.org/rules.htm).
[3]The NRC's "Guide for the Care and Use of Laboratory Animals" (1996).

Cost to Respondents

The estimated annual cost to respondents is $7,194.04.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	7.27	$50.00	$363.50
Recordkeeping	148.49	$46.00	$6,830.54
TOTAL			$7,194.04

The reporting cost estimate is based on an average pay rate of $50.00/hour. This average is based on the salaries of an upper-level manager, mid-level professional, and clerical support who may be involved in notifying or providing any necessary information. The recordkeeping cost estimate is based on an average pay rate of $46.00/hour of a study coordinator and clinical investigator who are involved with the documentation and maintenance of records. The salary estimates include benefits but no overhead costs.

13. Capital Costs (Maintenance of Capital Costs)

There are no capital costs or operating and maintenance costs associated with this collection of information.

14. Cost to Federal Government

The estimated annual cost to FDA is $3,440.00.

Activity	Number of Inspections	Review Time	Average Cost per Hour	Total Cost
Review / Inspection	0-1 (1)	40 hrs.	$86.00	$3,440.00

The cost to the Federal Government is based on two FDA investigators at an average grade scale of GS 13 ($43.00/hr) who perform on-site inspections. The salary estimate includes benefits but no overhead costs. The cost is also based on an average time to inspect a facility, review the records, and prepare an establishment inspection report. FDA has not inspected any sponsor or source animal facility and does not plan to inspect them unless the need arises due to specific circumstances. Therefore, FDA is estimating one annual inspection.

15. Program or Burden Changes

The previous burden estimate was 156.26 hours. The burden estimate is 155.76 hours. The slight decrease in burden is insignificant since there have been no changes in the requirements for the reporting and recordkeeping systems, and that the limited number of clinical studies with small patient populations has not changed over the last few years.

16. Publication and Tabulation Dates

There are no results to publish for this information collection.

17. Display of OMB Approval Date

FDA is not seeking approval to exempt the display of the expiration date of the OMB approval.

18. Exceptions to "Certification for Paperwork Reduction Act Submissions"

There are no exceptions to Item 19 of OMB Form 83-I.