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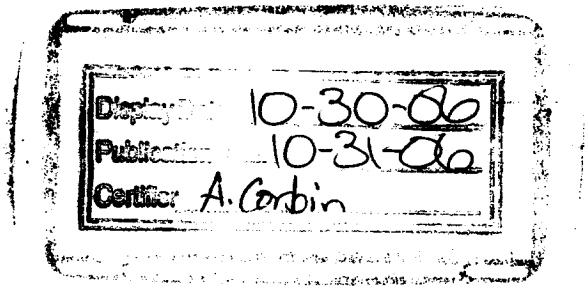

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2006N–0239]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Infectious Disease Issues in Xenotransplantation

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT: Jonna Capezzuto, Office of the Chief Information Officer (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4659.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

oc06243 2006N-0239 H2

Infectious Disease Issues in Xenotransplantation—(OMB Control Number 0910–0456)—Extension

The statutory authority to collect this information is provided under sections 351 and 361 of the Public Health Service (PHS) act (42 U.S.C. 262 and 264) and the provisions of the Federal Food, Drug, and Cosmetic Act that apply to drugs (21 U.S.C. 301 *et seq.*). 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 guideline is intended to provide general guidance to sponsors in the following ways: (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 guideline also describes a public health need for a national xenotransplantation database, which is currently under development by PHS. The PHS guideline is intended to protect the public health and to help ensure the safety of using xenotransplantation products in humans by preventing the introduction,

transmission, and spread of infectious diseases associated with xenotransplantation.

The PHS guideline also recommends that certain specimens and records be maintained for 50 years beyond the date of the xenotransplantation. These include the following information, as recommended by the specific PHS guideline sections: (1) Records linking each xenotransplantation product recipient with relevant health records of the source animal, herd, or colony, and the specific organ, tissue, or cell type included in or used in the manufacture of the product (3.2.7.1); (2) aliquots of serum samples from randomly selected animal and specific disease investigations (3.4.3.1); (3) source animal biological specimens designated for PHS use (3.7.1); animal health records (3.7.2), including necropsy results (3.6.4); and (4) recipients' biological specimens (4.1.2). 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.

The recommendation for maintaining records for 50 years is based on clinical experience with several human viruses that have presented problems in human to human transplantation and are therefore thought to share certain characteristics with viruses that may pose potential risks in xenotransplantation. These characteristics include long latency periods and the ability to establish persistent infections. Several also share the possibility of transmission among individuals through intimate contact with human body fluids. Human immunodeficiency virus (HIV) and Human T-lymphotropic virus are human retroviruses. Retroviruses contain ribonucleic acid (RNA) that is reverse-transcribed into deoxyribonucleic acid (DNA) using an enzyme

provided by the virus and the human cell machinery. That viral DNA can then be integrated into the human cellular DNA. Both viruses establish persistent infections and have long latency periods before the onset of disease, 10 years and 40 to 60 years, respectively. The human hepatitis viruses are not retroviruses, but several share with HIV the characteristic that they can be transmitted through body fluids, can establish persistent infections, and have long latency periods, e.g., approximately 30 years for Hepatitis C.

In addition, the PHS guideline recommends that a record system be developed that allows easy, accurate, and rapid linkage of information among the specimen archive, the recipient's medical records, and the records of the source animal for 50 years. The development of such a record system is a one-time burden. Such a system is intended to cross-reference and locate relevant records of recipients, products, source animals, animal procurement centers, and nosocomial exposures.

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 that 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.

FDA is requesting an extension of OMB approval for the following reporting and recordkeeping recommendations in the PHS guideline:

TABLE 1.—REPORTING RECOMMENDATIONS

PHS Guideline Section	Description
3.2.7.2	Notify sponsor or FDA of new archive site when the source animal facility or sponsor ceases operations
3.4	Standard operating 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

PHS Guideline Section	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 nosocomial exposures)
3.4.2	Document results of monitoring program used to detect introduction of infectious agents which 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

FDA estimates the burden for this collection of information as follows:

TABLE 3.—ESTIMATED ANNUAL REPORTING BURDEN[1]

PHS Guideline Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
3.2.7.2[2]	1	1	1	0.5	0.5
3.4[3]	12	0.33	4	0.08	0.32

TABLE 3.—ESTIMATED ANNUAL REPORTING BURDEN[1]—Continued

PHS Guideline Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
3.5.1[4]	12	0.08	(0–1) 1	0.25	0.25
3.5.4[5]	12	1	12	0.5	6.0
3.5.5[4]	18	0.06	(0–1) 1	0.2	0.2
Total					7.27

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.
[2]No animal facility or sponsor has ceased operations in the last 3 years, however, we are using 1 respondent for estimation purposes.
[3]FDA's records indicate that an average of 4 INDs are expected to be submitted per year.
[4]To our knowledge, has not occurred in the past 3 years and is expected to continue to be a rare occurrence.
[5]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[1]

PHS Guideline Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
3.2.7[2]	1	1	1	16	16
4.3[3]	12	1	12	0.83	9.96
3.4.2[4]	12	11	132	0.25	33
3.4.3.2[5]	18	4	72	0.3	21.6
3.5.1[6]	12	0.08	(0–1) 1	0.5	0.5
3.5.2[6]	12	0.08	(0–1) 1	0.25	0.25
3.5.4	12	1	12	0.17	2.04
3.6.4[7]	12	2	24	0.25	6
3.7[7]	18	1.33	24	0.08	1.92
4.2.3.2[8]	12	25	300	0.17	51
4.2.3.2[6]	12	0.08	(0–1) 1	0.17	0.17
4.2.3.3 and 4.3.2[6]	12	0.08	(0–1) 1	0.17	0.17
4.3.1	12	1	12	0.25	3
5.2[9]	12	3	36	0.08	2.88
Total					148.49

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.
[2]A 1-time burden for new respondents to set up a recordkeeping system linking all relevant records. FDA estimates 1 new sponsor annually.
[3]FDA estimates there is minimal recordkeeping burden associated with maintaining the record system.
[4]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 7 of this table); 108 + 24 = 132 monitoring records to document.
[5]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.
[6]Has not occurred in the past 3 years and is expected to continue to be a rare occurrence.
[7]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 5 of table 3 of this document).
[8]FDA estimates there are approximately 12 clinical centers doing xenotransplantation procedures x approximately 25 health care workers involved per center = 300 health care workers.
[9]24 source animal records + 12 recipient records = 36 total records.

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.

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 follows: (1) "Current Good Manufacturing Practice for Finished Pharmaceuticals," 21 CFR 211.1 through 211.208, approved through September 30, 2008, under OMB control number 0910–0139; (2) "Investigational New Drug Application," 21 CFR 312.1 through 312.160, approved through May 31, 2009, under OMB control number 0910–0014; and (3) information included in a license application, 21 CFR 601.2, approved through September 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 that reflect industry's usual and customary business practice.

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, and contacts	312.62(c)
3.1.1 and 3.1.6	Document well-characterized health history and lineage of source animals	312.23(a)(7)(a) 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

TABLE 5.—COLLECTION OF INFORMATION REQUIRED BY CURRENT REGULATIONS AND STANDARDS—Continued

PHS Guideline Section	Description of Collection of Information Activity	21 CFR Section (Unless Otherwise Stated)
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's) 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 lifelong (justify > 2 years (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/accreditation/rules.cfm*). (FDA has verified the Web site address, but is not responsible for subsequent changes to the Web site address after this document publishes in the **Federal Register**.)
[3]NRC's "Guide for the Care and Use of Laboratory Animals" (1996).

In the **Federal Register** of June 22, 2006 (71 FR 35911), FDA published a 60-day notice requesting public comment on the information collection provisions. No comments were received.

Dated: 10/24/06

October 24, 2006.

Jeffrey Shuren

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 06–????? Filed ??–??–06; 8:45 am]

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