United States Food and Drug Administration

Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation

OMB Control No. 0910-0456

SUPPORTING STATEMENT

Terms of Clearance: None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

This information collection supports Food and Drug Administration (FDA, us or we) guidance. The document entitled "Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation" (PHS Guideline) is available from our website at https://www.fda.gov/media/73803/download. See Appendix A for a list of guideline citations covered by this information collection.

The Food and Drug Administration is authorized to collect this information under sections 351 and 361 of the Public Health Service Act (PHS Act, 42 U.S.C. 262 and 264) and provisions of the Federal Food, Drug, and Cosmetic Act that apply to drugs (21 U.S.C. 301 et seq.). The guideline was developed by the PHS to identify general principles for the prevention and control of infectious diseases associated with xenotransplantation that may pose a risk to public health.

We request OMB approval of the information collection provisions found in the PHS Guideline, as discussed in this supporting statement.

2. Purpose and Use of the Information Collection

The PHS Guideline recommends procedures to diminish the risk of transmission of infectious agents to the xenotransplantation product recipient and to 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 collections of information described in this PHS Guideline include the notification of certain information to FDA or to the sponsor, and documentation of certain information associated with xenotransplantation. The collections of information are intended to provide general guidance on the following topics: (1) The development of xenotransplantation clinical protocols, (2) the preparation of submissions to FDA, and (3) the conduct of xenotransplantation clinical trials. Also, the collections of information are intended to 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 also 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 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.

3. Use of Improved Information Technology and Burden Reduction

Sponsors may record and store data and information electronically. Notification may be made by phone, fax, mail or e-mail. FDA believes that the increased use of electronic data storage and notification will enhance the timeliness, effectiveness, and efficiency. We are not aware of any other improved technology to reduce the burden. We continue to pursue methods of applying technology to reduce the burden to the respondents of the information collection.

4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of duplicative information collection.

5. Impact on Small Businesses or Other Small Entities

Although FDA must apply the statutory and regulatory requirements equally to all enterprises, FDA does provide special help to small businesses. CBER's Office of Communication, Outreach, and Development, Division of Manufacturers Assistance and Training, provides assistance to small businesses subject to FDA's regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

The recommendations provided in the PHS Guideline are intended to diminish the risk of transmission of infectious agents to the xenotransplantation product recipient, to health care workers, 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, to health care workers and to the general public.

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

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

A sponsor may be required to submit to FDA proprietary trade secret or other confidential information when providing requested information. The confidentiality of information received by FDA is consistent with the Freedom of Information Act (FOIA) and the agency's published regulations of "Public Information" under 21 CFR Part 20.

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 PHS 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. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In the *Federal Register* of October 22, 2021 (86 FR 58666), FDA published a 60-day notice requesting public comment on the proposed collection of information. FDA received one comment letter, which contained multiple comments, in response to the notice. Comments that were non-responsive to the four information collection topics solicited in our 60-day notice (recommendations for selection of xenograft recipients, hospital personnel and care providers, and handling of donor and recipient tissue) were not addressed in our 30-day notice; however, those comments that were responsive were discussed and our responses are included here:

(Comment 1) One comment in the letter was supportive of expanded collection and testing of blood samples from xenograft recipients, their immediate family, close social/sexual contacts, as well as other persons at risk of exposure to infection.

(Response) We agree with the utility of blood sampling and testing to track the source of any long-term developing infections as result of xenotransplantation. We have considered the comment and have determined that the comment does not present information that would warrant substantive changes to the guideline at this time.

(Comment 2) One comment in the letter recommended shortening the 50-year retention period for frozen samples of serum, cells, and tissues recommended by the PHS guideline. Among other reasons, the comment argued that transplant recipients generally manifest either donor-derived or opportunistic infections in the first-year post-transplantation; malignancies and uncommon infections may manifest later, but generally within 5-10 years; and patient survival post-organ transplantation is generally less than 20 years. The comment concluded that storage of samples beyond 20 years for initial studies should not be necessary.

(Response) We have considered the comment and have determined that the comment does not present information that would warrant substantive changes to the guideline at this time.

(Comment 3) One comment in the letter stated that the sponsor of the clinical trial or the hospital in which the trial is carried out should be relieved of the responsibility to store their records and samples. The comment argued that ongoing data and specimen collection, as well as the maintenance of repositories represents a significant burden on both sponsors and transplant programs with resultant significant cost and hardship that could deter xenotransplant progress. The comment concluded that storage of records and samples should be the responsibility of a recognized government authority or institution or an FDA-designated organization. The

comment recommended the creation of a central repository for both data and specimen collection run by, or under contract with, the federal government.

(Response) The comment did not provide any data that would support a change to the burden estimate in the 60-day notice. Thus, FDA has not changed the burden estimate in table 1 of this document. We have considered the comment and have determined that the comment does not present information that would warrant substantive changes to the guideline at this time.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift was provided to respondents.

10. Assurance of Confidentiality provided to Respondents

In preparing this Supporting Statement, we consulted our Privacy Office to ensure appropriate identification and handling of information collected.

This ICR collects personally identifiable information (PII). PII is collected in the context of the subject individuals' professional capacity and the FDA-related work they perform for their employer (e.g., point of contact at a regulated entity). The PII submitted to FDA is contact information and might include name, address, telephone number, email address and fax number. Xenotransplantation product receipt records are maintained by the firm and not submitted to the FDA. Information submitted to FDA is to notify of a new archive site when the source animal facility or sponsor ceases operation. FDA determined that although PII is collected it is not subject to the Privacy Act of 1974 and the particular notice and other requirements of the Act do not apply. Specifically, FDA does not use name or any other personal identifier to retrieve records from the information collected.

Under the Freedom of Information Act (FOIA) (5 U.S.C. 552), the public has broad access to government documents. However, FOIA provides certain exemptions from mandatory public disclosure of government records (5 U.S.C. 552(b)(1-9)).

11. Justification for Sensitive Questions

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

12. Estimates of Annualized Burden Hours and Costs

The total estimated annual burden for this collection of information is 59.03 hours.

12a. Annualized Hour Burden Estimate

Table 1-Estimated Annual Reporting Burden					
PHS Guideline Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
3.2.7.2[1]	1	1	1	0.50 (30 minutes)	0.50

[1] FDA is using one animal facility or sponsor for estimation purposes.

Table 2-Estimated Annual Recordkeeping Burden					
PHS Guideline Section	Number of Recordkeepers	Number of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
3.2.7[1]	1	1	1	16	16
4.3[2]	3	1	3	0.75 (45 minutes)	2.25
3.4.2[3]	3	10.67	32	0.25 (15 minutes)	8
3.4.3.2[4]	3	2.67	8	0.25 (15 minutes)	2
3.5.1[5]	3	0.33	1	0.50 (30 minutes)	0.50
3.5.2[5]	3	0.33	1	0.25 (15 minutes)	0.25
3.5.4	3	1	3	0.17 (10 minutes)	0.51
3.6.4[6]	3	2.67	8	0.25 (15 minutes)	2
3.7[6]	4	2	8	0.08 (5 minutes)	0.64
4.2.3.2[7]	5	25	125	0.17 (10minutes)	21.25
4.2.3.2[5]	5	0.20	1	0.17 (10 minutes)	0.17
4.2.3.3 and 4.3.2[5]	5	0.20	1	0.17 (10 minutes)	0.17
4.3.1	3	1	3	0.25 (15 minutes)	0.75
5.2[8]	3	4	12	0.08 (5 minutes)	0.96
Total					55.45

[1] A one-time burden for new respondents to set up a recordkeeping system linking all relevant records. FDA is using one new sponsor for estimation purposes.
[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 4 facilities = 24 sentinel animals. There are approximately 8 source animals per year (see footnote 6 of this table); 24 + 8 = 32 monitoring records to document.
[4] Necropsy for animal deaths of unknown cause estimated to be approximately 2 per herd per year x 1 herd per facility x 4 facilities = 8.
[5] Has not occurred in the past 3 years and is expected to continue to be a rare occurrence.
[6] On average two 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 4 recipients annually = 8 source animals per year. (See footnote 4 of table 3 of this document)

[7] FDA estimates there are approximately 5 clinical centers doing xenotransplantation procedures x approximately 25 health care workers involved per center = 125 health care workers.
[8] Eight source animal records + 4 recipient records = 12 total records.

Table 3-Estimated Annual Third-Party Disclosure Burden					
PHS Guideline Section	Number of Respondents	Number of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
3.2.7.2[1]	1	1	1	0.50 (30 minutes)	0.50
3.4[2]	4	0.25	1	0.08 (5 minutes)	0.08
3.5.1[3]	4	0.25	1	0.25 (15 minutes)	0.25
3.5.4[4]	4	1	4	0.50 (30 minutes)	2.00
3.5.5[3]	4	0.25	1	0.25 (15 minutes)	0.25
Total					3.08

[1] FDA is using one animal facility or sponsor for estimation purposes.
[2] FDA's records indicate that an average of 1 INDs is 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 12 patients treated over a 3-year period, the average number of xenotransplantation product recipients per year is estimated to be 4.

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. The FDA investigational related applications database tracks the number of INDs and the sponsors of the INDs and is used to determine the number of active files and the sponsors of the files. Based on data retrieved from that system, there are an estimated 3 respondents who are sponsors of INDs that include protocols for xenotransplantation in humans and 5 clinical centers doing xenotransplantation procedures. Based on FDA's institutional knowledge, other respondents for this collection of information are an estimated 4 source animal facilities which provide source xenotransplantation product material to sponsors for use in human xenotransplantation procedures. These 4 source animal facilities keep medical records of the herds/colonies as well as the medical records of the individual source animal(s). The burden estimates are based on FDA's institutional knowledge and records of xenotransplantation-related INDs and estimates of time required to complete the various reporting, recordkeeping, and third-party disclosure tasks described in the PHS Guideline.

Information collections in this guideline not included in tables 1 through 3, or listed in Appendix A, 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 under OMB control number 0910-0139; (2) "Investigational New Drug Application," 21 CFR 312.1 through 312.160, approved under OMB control number 0910-0014; and (3) information included in a biologics license application, 21 CFR 601.2, approved 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 3.

In table 4 of this document, FDA identifies those collections of information activities that are already encompassed by existing regulations or are consistent with voluntary standards which reflect industry's usual and customary business practices.

Table 4-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 ensures counseling patient + family + 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
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	312.23(a)(6)(iii)(f) and (a)(6)(iii) (g), and 312.62(b)

	life-long (justify >2 yrs.); investigator case histories (2 yrs. after investigation is discontinued)	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 investigations properly)	312.50
4.3	Sponsor to keep records of receipt, shipment, and disposition of investigational 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" (https://olaw.nih.gov/policies-laws/phs-policy.htm).
[2]AAALAC International Rules of Accreditation (https://www.aaalac.org/accreditation-program/rules-of-accreditation/).
[3]The NRC's "Guide for the Care and Use of Laboratory Animals."

12b. Annualized Cost Burden Estimate to Respondents

The estimated annual cost to respondents is $4,323.51.

Activity	Total Burden Hours	Hourly Wage Rate	Total Cost
Reporting	0.50	$77.00	$38.50
Recordkeeping	55.45	$73.00	$4,047.85
Disclosure	3.08	$77.00	$237.16
TOTAL			$4,323.51

The reporting cost estimate is based on an average pay rate of $77.00/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 $73.00/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. Estimates of Other Total Annual Costs to Respondents/Recordkeepers or Capital Costs

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

14. Annualized Cost to the Federal Government

The estimated annual cost to FDA is $4,880.00.

Activity	Number of Inspections	Review Time	Average Cost per Hour	Total Cost
Review / Inspection	1	40 hrs.	$122.00	$4,880.00

The cost to the Federal Government is based on two FDA investigators at an average grade scale of GS-13 ($61.00/hour) 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 does not plan to inspect them unless the need arises due to specific circumstances. Therefore, FDA is estimating one annual inspection.

15. Explanation for Program Changes or Adjustments

The total estimated annual burden is 59.03 hours. Based on a review of the information collection since our last request for OMB approval, we have made no adjustments to our burden estimate other than to adjust total burden hours by one hour, from 60 to 59 total burden hours, to address an inadvertent error in disclosure burden in the previous submissions to OMB.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

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

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.

Appendix A

The 0910-0456 information collection includes the following citations in the PHS Guideline, as well as other provisions, as discussed in this supporting statement:

Table A1-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.

Table A2-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 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 or eliminating 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 recipients and source animals.

Table A3-Disclosure 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 documented and available to review bodies.
3.5.1	Include increased infectious risk in informed consent if source animal quarantine period of 3 weeks is shortened or eliminated.
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 the clinical center when infectious agent is identified in source animal or herd after xenotransplantation product procurement.