UNITED STATES FOOD & DRUG ADMINISTRATION

Public Health Service Guideline on
Infectious Disease Issues in Xenotransplantation

OMB Control No. 0910-0456

SUPPORTING STATEMENT **Part A – Justification**:

1. Circumstances Making the Collection of Information Necessary

This information collection supports implementation of sections 351 and 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 262 and 264) and certain drug provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.). In the Federal Register of January 29, 2001 (66 FR 8120), the Food and Drug Administration (FDA, us or we) announced the availability of the "*PHS Guideline on Infectious Disease Issues in Xenotransplantation*." 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. The PHS guideline recommends procedures to diminish the risk of transmission of infectious agents to the xenotransplantation product recipient and to the general public.

In 2001, FDA on behalf of PHS announced the PHS Guideline to address the infectious disease concerns raised by xenotransplantation. The PHS Guideline was jointly developed by agencies within the Department of Health and Human Services (DHHS), including FDA, the Centers for Disease Control and Prevention, the Health Resources and Services Administration, the National Institutes of Health, all parts of PHS 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.

The PHS Guideline covers information collection provisions including notification of certain information to FDA or to sponsors, 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.

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

2. Purpose and Use of the Information Collection

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. Respondents to the collection are 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.

3. Use of Improved Information Technology and Burden Reduction

Respondents to the information collection may use computerized storage e.g., (tapes, discs, etc.), 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. Although we are unaware of any other improved technology to further reduce the burden, we continue to pursue methods of applying technology to further reduce the burden to the respondents of the collection of information.

4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of duplicative information collection. The provisions of the PHS Guideline uniquely apply to Infectious Disease Issues in Xenotransplantation.

5. Impact on Small Businesses or Other Small Entities

The information collection imposes no undue burden on small entities. At the same time, assistance is available to small business entities through our Center for Biologics Evaluation and Research's (CBER's) Office of Communication, Outreach, and Development, Division of Manufacturers Assistance and Training, as well as through resources available from our website.

6. Consequences of Collecting the Information Less Frequently

The information collection schedule recommended is 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.

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

Because xenotransplantation is a unique area of medical science where potential problems and adverse effects continue to be revealed. Due to the potential risk for cross-species transmission of pathogenic persistent virus, the PHS Guideline recommends that health records be retained for 50 years. We regard these records as "*[f]acts or opinions obtained initially or in follow-on requests, from individuals (including individuals in control groups) under treatment or clinical examination*" (5 CFR 1320.3(h)(5)) and therefore not subject to OMB review. The retention

period is intended to assist health care practitioners and officials in surveillance and tracking sources of infection, disease, or illness that might emerge in recipients, 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 Agency

In accordance with 5 CFR 1320.8(d), we published a 60-day notice inviting public comment in the Federal Register of September 25, 2018 (83 FR 48441). No comments were received.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift is provided to respondents.

10. Assurance of Confidentiality Provided to Respondents

Proprietary trade secret or other confidential information may be submitted consistent with provisions found in the guideline. 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.

11. Justification for Sensitive Questions

There are no questions of a sensitive nature associated with the information collection.

12. Estimates of Annualized Burden and Costs

We estimate the burden for the information collection as follows:

12a. Annualized Hour Burden Estimate

The total estimated annual hourly burden is 59.03, as reflected in the tables below:

Table 1 – Estimated Annual Reporting Burden[1]

PHS Guideline Section; Information Collection Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Avg. Burden per Response	Total Hours
3.2.7.2; Notify sponsor or FDA of new archive site when the source animal facility or sponsor ceases operations.[2]	1	1	1	0.50 (30 mins.)	0.5

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] FDA is using 1 animal facility or sponsor for estimation purposes.

Table 2 – Estimated Annual Recordkeeping Burden[1]

PHS Guideline Section; Information Collection Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Avg. Burden per Recordkeeping	Total Hours
3.2.7; Establish records linking each xenotransplantation product recipient with relevant records.[2]	1	1	1	16	16
4.3; Sponsor to maintain cross-referenced system that links all relevant records (recipient, product, source animal, animal procurement center, and nosocomial exposures).[3]	3	1	3	0.75 (45 mins.)	2.25
3.4.2; Document results of monitoring program used to detect introduction of infectious agents which may not be apparent clinically.[4]	3	10.67	32	0.25 (15 mins.)	8
3.4.3.2; Document full necropsy investigations including evaluation for infectious etiologies.[5]	3	2.67	8	0.25 (15 mins.)	2
3.5.1; Justify shortening a source animal's quarantine period of 3 weeks prior to xenotransplantation product procurement.[6]	3	0.33	1	0.50 (30 mins.)	0.5
3.5.2; Document absence of infectious agent in xenotransplantation product if its presence elsewhere in source animal does not preclude using it.[6]	3	0.33	1	0.25 (15 mins.)	0.25
3.5.4; Add summary of individual source animal record to permanent medical record of the xenotransplantation product recipient.	3	1	3	0.17 (10 mins.)	0.51
3.6.4; Document complete necropsy results on source animals (50-year record retention).[7]	3	2.67	8	0.25 (15 mins.)	2
3.7; Link xenotransplantation product recipients to individual source animal records and archived biologic specimens.[7]	4	2	8	0.08 (5 mins.)	0.64
4.2.3.2; Record baseline sera of xenotransplantation health care workers and specific nosocomial exposure.[8]	5	25	125	0.17 (10 mins.)	21.25
4.2.3.2; Record baseline sera of xenotransplantation health care workers and specific nosocomial exposure (no exposure)..[6]	5	0.20	1	0.17 (10 mins.)	0.17
4.2.3.3 and 4.3.2; Keep a log of health care workers' significant nosocomial exposure(s).[6]	5	0.20	1	0.17 (10 mins.)	0.17
4.3.1; Document each xenotransplant procedure.	3	1	3	0.25 (15 mins.)	0.75
5.2; Document location and nature of archived specimens in health care records of xenotransplantation product recipient and source animal.[9]	3	4	12	0.08 (5 mins.)	0.96
Total					55.45

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

[2] A one-time burden for new respondents to set up a recordkeeping system linking all relevant records. FDA is using 1 new sponsor for estimation purposes.
[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 4 facilities = 24 sentinel animals. There are approximately 8 source animals per year (see footnote 7 of this table); 24 + 8 = 32 monitoring records to document.
[5] 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.
[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 4 recipients annually = 8 source animals per year. (See footnote 5 of table 6 of this document.)
[8] FDA estimates there are 5 clinical centers doing xenotransplantation procedures x approximately 25 health care workers involved per center = 125 health care workers.
[9] Eight source animal records + 4 recipient records = 12 total records.

Table 3 – Estimated Annual Third-Party Disclosure Burden[1]

PHS Guideline Section; Information Collection Activity	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Avg. Burden per Disclosure	Total Hours
3.2.7.2; Notify sponsor or FDA of new archive site when the source animal facility or sponsor ceases operations.[2]	1	1	1	0.50 (30 mins.)	0.5
3.4; Standard operating procedures (SOPs) of source animal facility should be available to review bodies.[3]	4	0.25	1	0.08 (5 mins.)	0.08
3.5.1; Include increased infectious risk in informed consent if source animal quarantine period of 3 weeks is shortened.[4]	4	0.25	1	0.25 (15 mins.)	0.25
3.5.4; Sponsor to make linked records described in section 3.2.7 available for review.[5]	4	1	4	0.50 (30 mins.)	2
3.5.5; Source animal facility to notify clinical center when infectious agent is identified in source animal or herd after xenotransplantation product procurement.[4]	4	0.25	1	0.25 (15 mins.)	0.25
Total					3.08

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] FDA is using 1 animal facility or sponsor for estimation purposes.
[3] FDA's records indicate that an average of 1 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 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 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 three respondents who are sponsors of INDs that include protocols for xenotransplantation in humans and five clinical centers doing xenotransplantation procedures. Other respondents for this collection of information are an estimated four source animal facilities which provide source xenotransplantation product material to sponsors for use in human

xenotransplantation procedures. These four 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 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.

12b. Annualized Cost Burden Estimate

The estimated annual cost burden is $3,921.04, as reflected below.

Activity	Total Burden Hours	Hourly Wage Rate	Total Cost
Reporting	0.50	$73.00	$36.50
Recordkeeping	55.45	$66.00	$3,659.70
Disclosure	3.08	$73.00	$224.84
TOTAL			$3,921.04

The reporting cost estimate is based on an average pay rate of $73.00/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 $66.00/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 Cost Burden to Respondents or Recordkeepers

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

Costs to FDA covers the allocation of two investigators at an average cost commensurate with the pay of a grade scale (GS)-13 ($58.00/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. Based on our experience with the collection, we expect to incur costs for one inspection annually. Cumulatively therefore, the total cost is $4,640.00 (1 inspection utilizing 2 investigators @ $58/hr. for 40 hours = $4,640.00)

15. Explanation for Program Changes or Adjustments

Based on our evaluation of the information collection, we are retaining the currently approved burden estimate. At the same time, we have consolidated the itemized listing of IC elements into three discrete ICs reflecting notification (reporting), recordkeeping, and disclosure. Finally, we have uploaded costs found in *Question 12b*, previously and currently included, so that they are reflected at www.reginfo.gov for easier reference by our readers.

16. Plans for Tabulation and Publication and Project Time Schedule

We have no such plans for the information collection.

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

The OMB expiration date will be displayed as required.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.