II. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

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*2. Arroyo, R., A.P. Sempere, E. Ruiz-Beato, et al. (2017). ''Conjoint Analysis to Understand Preferences of Patients With Multiple Sclerosis for Disease-Modifying Therapy Attributes in Spain: A Cross-Sectional Observational Study.'' *BMJ Open,* 7(3), e014433. *https://doi.org/10.1136/bmjopen-2016-014433.*

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5. Wouters, H., G.A. Maatman, L. Van Dijk, et al. (2013). ''Trade-Off Preferences Regarding Adjuvant Endocrine Therapy Among Women With Estrogen Receptor-Positive Breast Cancer.'' *Annals of Oncology,* 24(9), 2324–2329. *https://doi.org/10.1093/annonc/mdt195.*

6. Gregorian, Jr., R.S., A. Gasik, W.J. Kwong, et al. (2010). ''Importance of Side Effects in Opioid Treatment: A Trade-Off Analysis With Patients and Physicians.'' *The Journal of Pain,* 11(11), 1095–1108. *https://doi.org/10.1016/j.jpain.2010.02.007.*

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Dated: April 19, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022–08728 Filed 4–22–22; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2012–N–0559]

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

AGENCY: Food and Drug Administration, Health and Human Services (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: Submit written comments (including recommendations) on the collection of information by May 25, 2022.

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be submitted to *https://www.reginfo.gov/public/do/PRAMain.* Find this particular information collection by selecting ''Currently under Review—Open for Public Comments'' or by using the search function. The OMB control number for this information collection is 0910–0456. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Rachel Showalter, Office of Operations, Food and Drug Administration, Three White Flint North, 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 240–994–7399, *PRAStaff@fda.hhs.gov.*

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.

Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation

OMB Control Number 0910–0456—Extension

This information collection helps support implementation of the Department of Health and Human Services' ''PHS Guideline on Infectious Disease Issues in Xenotransplantation'' dated January 19, 2001, available at: *https://www.fda.gov/media/73803/download.* FDA is authorized to collect this information under sections 351 and 361 of the 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. 321 *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. 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 collection of information described in this guideline is 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 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 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.

The PHS guideline also recommends that certain specimens and records be maintained for 50 years beyond the date of the xenotransplantation. These include: (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); (4) animal health records (3.7.2), including necropsy results (3.6.4); and (5) 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, such as human cytomegalovirus and BK polyoma virus, which 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 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 significant 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 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.

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. Several comments (recommendations for selection of xenograft recipients, hospital personnel and care providers, and handling of donor and recipient tissue) were not responsive to the four information collection topics solicited in the 60-day notice and therefore will not be addressed in this notice.

(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 a 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.

FDA is requesting an extension of OMB approval for the following reporting, recordkeeping and third-party

disclosure 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.

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 baseline 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 specimens in health care records of xenotransplantation product recipient and source animal.

TABLE 3—DISCLOSURE 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.

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

TABLE 4—ESTIMATED ANNUAL REPORTING BURDEN [1]

PHS guideline section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
3.2.7.2 [2]	1	1	1	0.5 (30 minutes)	0.5

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

TABLE 5—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

PHS guideline section	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
3.2.7 [2]	1	1	1	16	16
4.3 [3]	3	1	3	0.75 (45 minutes)	2.25
3.4.2 [4]	3	10.67	32	0.25 (15 minutes)	8
3.4.3.2 [5]	3	2.67	8	0.25 (15 minutes)	2
3.5.1 [6]	3	0.33	1	0.5 (30 minutes)	0.50
3.5.2 [6]	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 [7]	3	2.67	8	0.25 (15 minutes)	2
3.7 [7]	4	2	8	0.08 (5 minutes)	0.64

TABLE 5—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]—Continued

PHS guideline section	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
4.2.3.2 [8]	5	25	125	0.17 (10 minutes) ..	21.25
4.2.3.2 [6]	5	0.2	1	0.17 (10 minutes) ...	0.17
4.2.3.3 and 4.3.2 [6]	5	0.2	1	0.17 (10 minutes) ...	0.17
4.3.1	3	1	3	0.25 (15 minutes) ..	0.75
5.2 [9]	3	4	12	0.08 (5 minutes)	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 one 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 × 1 herd per facility × 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 × 1 herd per facility × 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 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 × 4 recipients annually = 8 source animals per year. (See footnote 5 of table 6.)
[8] FDA estimates there are 5 clinical centers doing xenotransplantation procedures × approximately 25 health care workers involved per center = 125 health care workers.
[9] Eight source animal records + 4 recipient records = 12 total records.

TABLE 6—ESTIMATED ANNUAL THIRD-PARTY DISCLOSURE BURDEN [1]

PHS guideline section	Number of respondents	Number of disclosures per respondent	Total annual disclosures	Average burden per disclosure	Total hours
3.2.7.2 [2]	1	1	1	0.5 (30 minutes)	0.5
3.4 [3]	4	0.25	1	0.08 (5 minutes)	0.08
3.5.1 [4]	4	0.25	1	0.25 (15 minutes) ..	0.25
3.5.4 [5]	4	1	4	0.5 (30 minutes)	2
3.5.5 [4]	4	0.25	1	0.25 (15 minutes) ..	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 one animal facility or sponsor for estimation purposes.
[3] FDA's records indicate that an average of one IND is 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.

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 6 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 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 6.

In table 7, FDA identifies those collection of information activities that are already encompassed by existing regulations or are consistent with voluntary standards which reflect industry's usual and customary business practice.

TABLE 7—COLLECTION OF INFORMATION REQUIRED BY CURRENT REGULATIONS AND STANDARDS

PHS guideline section	Description	21 CFR section (unless otherwise stated)
2.2.1	Document offsite collaborations	312.52.
2.5	Sponsor ensures counseling patient + family + contacts	312.62(c).

TABLE 7—COLLECTION OF INFORMATION REQUIRED BY CURRENT REGULATIONS AND STANDARDS—Continued

PHS guideline section	Description	21 CFR section (unless otherwise stated)
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 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'' (*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.''

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.

Dated: April 19, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022–08737 Filed 4–22–22; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–N–0413]

Baxter Healthcare Corporation, et al.; Withdrawal of Approval of 14 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, Health and Human Service (HHS).

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is withdrawing approval of 14 abbreviated new drug applications (ANDAs) from multiple applicants. The applicants notified the Agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

DATES: Approval is withdrawn as of May 25, 2022.

FOR FURTHER INFORMATION CONTACT: Martha Nguyen, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 1676, Silver Spring, MD 20993–0002, 240–402–6980, *Martha.Nguyen@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION: The applicants listed in the table have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications under the process described in § 314.150(c) (21 CFR 314.150(c)). The applicants have also, by their requests, waived their opportunity for a hearing. Withdrawal of approval of an application or abbreviated application under § 314.150(c) is without prejudice to refiling.