UNITED STATES FOOD AND DRUG ADMINISTRATION

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics

OMB Control No. 0910-0850

SUPPORTING STATEMENT

Terms of Clearance: None.

Part A: Justification:

1. Circumstances Making the Collection of Information Necessary

This information collection supports Food and Drug Administration (FDA, us or we) programs and guidance.

Section 2011 of the 21st Century Cures Act of 2016 (Pub. L. 114-255) encourages the FDA to develop new approaches for addressing regulatory science issues as part of the Precision Medicine Initiative (PMI).

In the Federal Register of January 17, 2018 (83 FR 2451), FDA announced the availability of a guidance for industry entitled "Use of Public Human Genetic Variant Databases To Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics."

The guidance document describes one part of FDA's PMI effort to create a flexible and adaptive regulatory approach to the oversight of next generation sequencing (NGS)-based tests. The goal of this effort is to help ensure patients receive accurate and meaningful test results, while promoting innovation in test development. The guidance document describes how publicly accessible databases of human genetic variants can serve as sources of valid scientific evidence to support the clinical validity of genotype-phenotype relationships in FDA's regulatory review of both NGS-based tests and genetic and genomic tests based on other technologies. Publicly accessible genetic databases may be useful to support the clinical validity of NGS tests as well as single gene or panel tests that use other technology.

The guidance describes FDA's considerations in determining whether a genetic variant database is a source of valid scientific evidence that could support the clinical validity of an NGS-based test. The guidance further outlines the process by which administrators[1] of genetic variant databases could voluntarily apply to FDA for recognition, and how FDA would review such applications and periodically reevaluate recognized databases. The guidance also recommends that, at the time of recognition, the database administrator make information regarding policies, procedures, and conflicts of interest publicly available and accessible on the genetic variant database's website.

We therefore request extension of OMB approval for the collection of information found in the guidance document "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics" as discussed in this supporting statement.

[1] FDA acknowledges that many databases may not use the term "administrator" or may have a committee of individuals that oversee the database. Therefore, for the purpose of this guidance, a genetic variant database administrator is the entity or entities that oversee database operations.

2. Purpose and Use of the Information Collection

The information collected under the guidance will be used by FDA to ensure the process by which administrators of genetic variant databases could voluntarily apply to FDA for recognition, and how FDA would review such applications and periodically reevaluate recognized databases.

FDA believes that the aggregation, curation, and evaluation of clinical genotype-phenotype associations in genetic variant databases could support the clinical validity of assertions made about a variant detected by a genetic or genomic-based test and a disease or condition. In relying on assertions in genetic variant databases that follow the recommendations in the guidance, FDA hopes to encourage the deposition of genetic variant information in such publicly accessible databases, reduce regulatory burden on test developers, and spur advancements in the evaluation and implementation of precision medicine.

The Agency believes such practices for evaluation of genetic variants help assure the quality of data and assertions within genetic variant databases and has built upon these approaches in developing the recommendations in the guidance.

FDA has long believed that public access to supporting data is important so that all interested persons (e.g., healthcare providers and patients) can make the most informed medical treatment decisions possible. To that end, for all IVDs that have received premarket clearance or De Novo classification from FDA since November 2003, FDA has published a Decision Summary that includes a review of the analytical and clinical validity data submitted by the applicant to support the submission and FDA's justification in clearing or classifying the IVD; FDA is also required to publish Summaries of Safety and Effectiveness Data for approved PMAs under Section 520(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA believes that similar public availability and access to data contained in genetic variant databases is important to patients and healthcare providers in order to make fully informed medical decisions.

FDA believes that if administrators of genetic variant databases follow the recommendations, including transparency regarding evidence evaluation, and obtain FDA recognition as described in the guidance, the data and assertions within would generally constitute valid scientific evidence that can be used to support clinical validity.

3. Use of Improved Information Technology and Burden Reduction

The guidance recommends that genetic variant database administrators seeking recognition of their genetic variant database contact FDA through the Q-Submission Program (see OMB control number 0910-0756). The submission is sent to FDA as an eCopy (CD, thumb drive, etc.) via U.S. mail. We expect that all submissions, recordkeeping, and third-party disclosures associated with this ICR will be in electronic format.

4. Efforts to Identify Duplication and Use of Similar Information

We are unaware of duplicative information collection. We are not aware of another agency or organization that provides recognition of genetic variant databases to support clinical validity for genetic and genomic-based in vitro diagnostics, the data and assertions within which would generally constitute valid scientific evidence that can be used to support clinical validity.

5. Impact on Small Businesses or Other Small Entities

Using the guidelines set by the Small Business Administration (SBA) on what constitutes a small business, for manufacturing, a small business cannot exceed 500 employees. Approximately 95% of U.S. medical device manufacturing establishments have under 500 employees.

FDA aids small businesses in dealing with the requirements of the regulations by providing assistance through its Division of Industry and Consumer Education (DICE), and through the scientific and administrative staff within the Center for Devices and Radiological Health. These efforts help to assure that the burden on small manufacturers is minimized. FDA also provides all manufacturers uniform device reporting criteria to avoid confusion and minimize burden to the respondent.

6. Consequences of Collecting the Information Less Frequently

Respondents will respond to the information collection occasionally.

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

There are no special circumstances for this collection of information.

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

In the Federal Register of September 23, 2020 (85 FR 59801), we published a 60-day notice requesting public comment on the proposed collection of information. FDA received two comments. One comment was not relevant to the topic or information collection. A summary of the other comment and our response are as follows:

(Comment) One comment expressed concerns and suggestions regarding the collection, storage, and security of personally identifiable information (PII) and protected health information (PHI).

(Response) The guidance document "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics" describes, among other things, FDA's considerations in determining whether a publicly accessible genetic variant database is a source of valid scientific evidence that could support the clinical validity of genetic and genomic-based tests in a premarket submission and outlines the process by which administrators of publicly accessible genetic variant databases could voluntarily apply to FDA for recognition, and how FDA would assess such applications and periodically reevaluate recognized databases. FDA recommends that genetic database administrators should identify the applicable laws and regulations to assure that any requirements are addressed and transparently documented. Genetic variant database administrators should also put in place adequate security measures to ensure the protection and privacy of PII and PHI and provide training for database staff on security and privacy protection. The guidance recommends that, among other considerations, such a genetic variant database would collect, store, and report data and conclusions in compliance with all applicable requirements regarding protected health information, patient privacy, research subject protections, and data security. In section V.A of the guidance, FDA discusses security and privacy of such data, stating that "[g]enetic variant database operations must be in compliance with all applicable federal laws and regulations (e.g., the Health Insurance Portability and Accountability Act, the Genetic Information Nondiscrimination Act, the Privacy Act, the Federal Policy for the Protection of Human Subjects ("Common Rule"), etc.) regarding protected health information, patient privacy, research involving human subjects, and data security, as applicable."

However, we believe the comment may misunderstand the subject of the information collection request (ICR). We are requesting extension of the OMB approval of the information collection associated with the guidance document, i.e., the application for recognition of a publicly accessible genetic variant database as a source of valid scientific evidence that could support the clinical validity of genetic and genomic-based tests in a premarket submission, as well as record maintenance and public disclosure related to such recognition. The application for recognition does not include submission of PII or PHI that may be contained in a genetic variant database. Rather, the application includes standard operating procedures and other documents related to the database's handling of PII and PHI confidentiality and privacy, among other considerations. The information collected in the application for recognition is used to evaluate the database's oversight and governance procedures to determine that, among other things, they are designed to ensure the protection of PII and PHI and provide appropriate training for database staff.

We have not revised the information collection based on the comment.

9. Explanation of Any Payment or Gift to Respondents

There are no incentives, payments or gifts associated with this information collection.

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 is names and credentials of individuals involved in the database (i.e. submission sponsors and provided points of contact). This collection is for standard operating procedures (SOPs) and other documents related to the database's handling of PII and protected health information confidentiality and privacy. These are publicly available genetic databases, and FDA evaluates the database's oversight and governance procedures for PII to determine that they are designed to ensure the protection of PII and PHI and provide appropriate training for database staff. FDA limited submission fields and minimized the PII collected to protect the privacy of the individuals.

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). FDA will make the fullest possible disclosure of records to the public, consistent with the rights of individuals to privacy, the property rights of persons in trade and confidential commercial or financial information.

11. Justification for Sensitive Questions

The collection of information does not involve sensitive questions.

12. Estimates of Annualized Burden Hours and Cost

12a. Annualized Hour Burden Estimate

Transparency and Public Accessibility: FDA recommends that genetic variant database administrators make publicly available sufficient information regarding data sources and standard

operating procedures (SOPs) for evaluation of evidence to allow FDA and the public to understand the criteria and processes used to collect and evaluate evidence about variants and enable patients and healthcare providers to make fully informed medical decisions.

Data Preservation: FDA recommends that genetic variant database administrators have processes in place for assessing overall database stability and architecture and for ensuring that data linkages are properly maintained. When a genetic variant database contains linkages to secondary databases, the genetic variant database administrator should have predefined processes in place to recognize changes to the secondary databases and account for them in version control of the primary database. FDA recommends genetic variant database administrators back-up the database on a regular basis so that it can be reinstated as necessary.

Genetic variant database administrators should have a plan in place to ensure database content and processes are preserved in the event a genetic variant database ceases operations permanently or temporarily (e.g., a database loses funding, infrastructure upgrades). A location to deposit data, including versioning information and supporting SOPs and documentation, in the event that the genetic variant database ceases operation should be identified.

To the extent possible or applicable, database administrators are required to submit metadata. This metadata should include information about the analytical performance of the test used to detect the variant, including the number of independent laboratories and/or studies reporting the variant, name of the laboratory(ies) that reported the variant, the name of the test used to detect the variant, and details of the technical characteristics of the test that was used (e.g., reference sequence version or build, instrument, software, bioinformatics tools, etc.). For germline variants, metadata should also include, to the extent possible, variant characteristics (which could include but is not limited to, patient ethnicity, zygosity, phasing, and segregation). For somatic variants, metadata should include, to the extent possible, additional information about the context in which the variant was detected (which could include but is not limited to, variant allele frequency, tumor only versus tumor-normal matched sequencing, cellularity). For cases in which multiple genetic variants factor into determining the overall risk of developing a disease or condition, database administrators should include any multivariant or polygenic scoring methods used in the metadata. As applicable, database administrators should also include as much information as is available regarding the contribution of environmental exposures to the development of a genotype-associated disease or condition. Genetic variant databases should clearly and transparently document evidence source(s) used to support variant assertions (e.g., literature, well-documented case histories). We believe databases administrators should make an effort to ensure no duplication within reason.

The following estimates are based on FDA's experience with Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostic Guidance FDA expects no more than 5 submissions for database recognition per year. Respondents are administrators of genetic databases. Our estimate of five respondents per year is based on the current number of databases that may meet FDA recommendations for recognition and seek such recognition.

Based on our experience and the nature of the information, we estimate that it will take an average of 80 hours to complete and submit an application for recognition. We estimate that maintenance of recognition activities will take approximately one-fourth of that time (20 hours) annually. We estimate that it will take approximately 1 hour to post the information on the website.

Table 1.--Estimated Annual Reporting Burden

Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Application for recognition of genetic database	5	1	5	80	400

Table 2.--Estimated Annual Recordkeeping Burden

Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
Maintenance of recognition activities	5	1	5	20	100

Table 3.--Estimated Annual Third-Party Disclosure Burden

Activity	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
Public disclosure of policies, procedures, and conflicts of interest	5	1	5	1	5

12b. Annualized Cost Burden Estimate

The estimated annual cost for a company to pay an employee to respond to the information collection is based on the average hourly salary of a database administrator multiplied by the total burden hours. The mean hourly wage cost is $46.21 per hour for Database Administrators and Architects (occupation code 15-1245), based on the "May 2019 National Occupational Employment and Wage Estimates United States" that is available at https://www.bls.gov/oes/current/oes_nat.htm#15-0000. We estimate that the average annualized burden cost for respondents is approximately $23,336 (rounded).

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Database administrators	505	$46.21	$23,336 (rounded)

13. Estimates of Other Total Annual Costs to Respondents/Recordkeepers or Capital Costs

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

14. Annualized Cost to the Federal Government

We expect that the scientific review staff (see section 14 of OMB control numbers 0910-0120, 0910-0231, and 0910-0078) will primarily conduct the recognition determinations with assistance from the PMI staff, as needed. We do not anticipate hiring any additional FTEs (full-time equivalent positions) to process this information collection.

15. Explanation for Program Changes or Adjustments*

Based on a review of the information collection since our last request for OMB approval, we have made no adjustments or program changes.

16. Plans for Tabulation and Publication and Project Time Schedule

This information collected will not be published or tabulated.

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

FDA will display the expiration date of OMB approval of the information collection.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.