This document is scheduled to be published in the
Federal Register on 04/13/2018 and available online at
https://federalregister.gov/d/2018-07686, and on **FDsys.gov**

4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-D-1233]

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics; Guidance for Stakeholders and Food and Drug Administration Staff; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of the final guidance entitled "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics; Guidance for Stakeholders and Food and Drug Administration Staff." This 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 genetic and genomic-based tests. This guidance further outlines 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.

DATES: The announcement of the guidance is published in the *Federal Register* on **[INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-D-1233 for "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics; Guidance for Stakeholders and Food and Drug Administration Staff." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff office between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

An electronic copy of the guidance document is available for download from the internet. See the SUPPLEMENTARY INFORMATION section for information on electronic access to the guidance. Submit written requests for a single hard copy of the guidance document entitled "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics; Guidance for Stakeholders and Food and Drug Administration Staff " to the Office of the Center Director, Guidance and Policy Development, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 5431, Silver Spring, MD 20993-0002, or the Office of Communication, Outreach, and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002 . Send one self-addressed adhesive label to assist that office in processing your request.

FOR FURTHER INFORMATION CONTACT: Laura Koontz, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4553, Silver Spring, MD 20993-0002, 301-796-7561, OIRPMGroup@fda.hhs.gov; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

This guidance document describes one part of FDA's effort to create a flexible regulatory approach to the oversight of genetic and genomic-based tests. FDA held three workshops on this issue: "Use of Databases for Establishing the Clinical Relevance of Human Genetic Variants" on November 13, 2015, "Patient and Medical Professional Perspectives on the Return of Genetic Test Results" on March 2, 2016, and "Adapting Regulatory Oversight of Next Generation Sequencing-Based Tests" on September 23, 2016. The goal of this effort is to help ensure patients receive accurate and meaningful results, while promoting innovation in test development. This 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 genetic and genomic-based tests. FDA is also issuing a guidance entitled "Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases--Guidance for Stakeholders and Food and Drug Administration Staff," which is being released concurrently elsewhere in this issue of the *Federal Register.*

NGS can enable rapid, broad, and deep sequencing of a portion of a gene, entire exome(s), or a whole genome and may be used clinically for a variety of diagnostic purposes, including risk prediction, diagnosis, and treatment selection for a disease or condition. The rapid adoption of NGS-based tests in both research and clinical practice is leading to identification of an increasing number of genetic variants (e.g., pathogenic, benign, and of unknown significance), including rare variants that may be unique to a single individual or family. This

guidance document 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 genetic and genomic based tests. This guidance further outlines 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. A draft guidance was announced in the *Federal Register* on July 8, 2016 (81 FR 44611) and made available for public comment. The comment period closed on October 6, 2016. FDA reviewed and considered all public comments received and revised the guidance as appropriate.

II. Significance of Guidance

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on the "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

III. Electronic Access

Persons interested in obtaining a copy of the guidance may do so by downloading an electronic copy from the internet. A search capability for all Center for Devices and Radiological Health guidance documents is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm. This guidance document is also available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm or https://www.regulations.gov. Persons unable to download an electronic copy of "Use of

Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics; Guidance for Stakeholders and Food and Drug Administration Staff" may send an email request to CDRH-Guidance@fda.hhs.gov to receive an electronic copy of the document. Please use the document number 16008 to identify the guidance you are requesting.

IV. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in the guidance document "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics; Guidance for Stakeholders and Food and Drug Administration Staff" have been approved under OMB control number 0910-0850. The collections of information in the guidance document "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff; Guidance for Industry and Food and Drug Administration Staff" have been approved under OMB control number 0910-0756. The collections of information regarding premarket submissions have been approved as follows: the collections of information in 21 CFR part 807, subpart E, have been approved under OMB control number 0910-0120 and the collections of information in 21 CFR part 814, subparts A through E, have been approved under OMB control number 0910-0231.

Dated: April 9, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018-07686 Filed: 4/12/2018 8:45 am; Publication Date: 4/13/2018]