



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-D-4267]

Biomarker Qualification: Evidentiary Framework; Draft Guidance for Industry and Food and Drug Administration Staff; Availability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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry and FDA staff entitled “Biomarker Qualification: Evidentiary Framework.” This draft guidance provides recommendations on general considerations to address when developing a biomarker for qualification under the 21st Century Cures Act (Cures Act), enacted on December 13, 2016, that added a new section to the Federal Food, Drug, and Cosmetic Act (FD&C Act). Qualification of a biomarker is a determination that within the stated context of use, the biomarker can be relied on to have a specific interpretation and application in drug development and regulatory review.

DATES: Submit either electronic or written comments on the draft guidance by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]** to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance 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-2018-D-4267 for "Biomarker Qualification: Evidentiary Framework; Draft Guidance for Industry and FDA

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 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)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Chris Leptak, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6461, Silver Spring, MD 20993-0002, 301-796-0017.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry and FDA staff entitled “Biomarker Qualification: Evidentiary Framework.” This draft guidance provides recommendations on general considerations to address when developing a biomarker for qualification under the Cures Act, enacted on December 13, 2016, that added a new section 507, Qualification of Drug Development Tools, to the FD&C Act (21 U.S.C. 357).¹ This guidance discusses the evidentiary framework that should be used to support biomarker qualification, as that term is now used in section 507 of the FD&C Act, and it was informed by public workshops that predated the Cures Act. Specifically, this guidance describes the needs assessment, context

¹ Section 507 of the FD&C Act was added by section 3011(a) of the Cures Act (Pub. L. 114-255).

of use, and benefit-risk considerations, and how these considerations can relate to determining the type and level of evidence to support qualification of a biomarker. This guidance also addresses general statistical and clinical considerations related to the correlation between the biomarker and the outcome of interest, as well as general analytical considerations related to the performance characteristics of the biomarker test.

Historically, biomarkers gained acceptance for use in drug development after evidence from scientific and medical communities accumulated over time, leading to the recognition of the role and value of the biomarker in decision making. This evidence was considered as part of drug-specific development efforts, and there was no formal regulatory process to assess the broader utility of the biomarker independent from its use in a specific drug program. Even after the Center for Drug Evaluation and Research established the legacy (pre-Cures Act) Biomarker Qualification Program in 2007, progress in the development of biomarkers and their application in drug development has been hampered by the lack of a clear, predictable, and specific regulatory framework for the evidence sufficient to support regulatory decision making using biomarkers. This guidance is an additional step towards informing future guidances that will specifically address this need, the Cures Act requirements, and commitments from the Prescription Drug User Fee Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022 (PDUFA VI goals letter)².

This guidance was informed by several public workshops³ that discussed the science to support biomarker qualification; these workshops convened before the enactment of the Cures

² The PDUFA VI goals letter is available at:

<https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>.

³ Workshops convened to discuss the science to support biomarker qualification included: Institute of Medicine Workshop on Biomarker Qualification (2009), FDA co-sponsored Biomarkers Workshop with Howard Hughes Medical Institute (2013), FDA co-sponsored Brookings meeting on Advancing the Use of Biomarkers and Pharmacogenomics (2014), FDA co-sponsored workshop with M-CERSI and the Critical Path Institute on

Act. Development of this guidance was also greatly facilitated by the efforts from the biomarker development community--including FDA, National Institutes of Health (NIH), industry, academia, patient groups, and the nonprofit sector--that developed an October 2016 white paper describing a Framework for Defining Evidentiary Criteria for Biomarker Qualification.⁴ In addition to considering public comments received regarding this guidance, FDA anticipates that the Agency will incorporate additional information required under the Cures Act and discussed in the PDUFA VI goals letter in a subsequent revised draft version of this guidance. Ultimately, FDA anticipates that a future revised draft guidance on this topic will meet the statutory requirement for guidance on a conceptual framework describing appropriate standards and scientific approaches to support the development of biomarkers as described in section 3011(b)(1)(A) of the Cures Act and meet the commitment in section (1)(J)(6)(d) of the PDUFA VI goals letter related to publishing a draft guidance on general evidentiary standards for biomarker qualification. As part of FDA's efforts to delineate the conceptual framework to support biomarker qualification and the general evidentiary standards for biomarker qualification, FDA also anticipates that subsequent guidance on biomarker qualification will address specific aspects of evidentiary considerations (e.g., statistical, analytical) in greater detail. This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115).

Evidentiary Considerations for Integration of Biomarkers in Drug Development (2015), NIH-FDA Workshop on Biomarker Glossary of Terms (2015), the National Biomarker Development Alliance's Workshop on Collaboratively Building a Foundation for FDA Biomarker Qualification (2015), and Foundation for the NIH-FDA Workshop on Developing an Evidentiary Criteria Framework for Safety Biomarkers Qualification (2016).

⁴ Biomarkers Consortium Evidentiary Standards Writing Group: Framework for Defining Evidentiary Criteria for Biomarker Qualification. Final version October 20, 2016. Available at: <https://fnih.org/sites/default/files/final/pdf/Evidentiary%20Criteria%20Framework%20Final%20Version%20Oct%2020%202016.pdf>.

The draft guidance, when finalized, will represent the current thinking of FDA on “Biomarker Qualification: Evidentiary Framework.” 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.

II. Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information that 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 21 CFR parts 312 and 314 have been approved under OMB control numbers 0910-0014 and 0910-0001, respectively.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <https://www.regulations.gov>.

Dated: December 7, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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