4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-D-4964]

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Revised Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing the availability of a revised draft guidance for industry titled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products." FDA has revised and is reissuing this draft guidance in response to public comments and to changes in drug development by focusing on generating rigorous scientific evidence in the most efficient manner. Advances in our understanding of biological processes and the increasing availability of high-quality data have transformed the evidentiary landscape for drug development. Given these advances, the draft guidance discusses the many factors that can impact the strength of evidence of effectiveness for a drug and clarifies how sponsors can rely on one adequate and well-controlled clinical investigation with confirmatory evidence to satisfy the substantial evidence of effectiveness standard. When final, this guidance will replace the 1998 guidance titled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products."

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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-2019-D-4964 for "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products." 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, 240-402-7500.

- 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.govinfo.gov/content/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, 240-402-7500.

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 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 or 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: Scott N. Goldie, Center for Drug Evaluation and Research, Food and Drug Administration, 301-796-2055, or Philip Kurs, Center for Biologics Evaluation and Research, Food and Drug Administration, 240-402-1279.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a revised draft guidance for industry titled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products." This draft guidance revises the draft guidance of the same name, which was announced in the *Federal Register* on December 20, 2019 (84 FR 70196) (the 2019 draft guidance). The substantial evidence of effectiveness standard ensures that the clinical evidence supporting a marketing application comes from clinical investigations that are adequate and well-controlled and from which FDA can conclude that the drug has its intended effect.

In 1998, FDA issued the seminal guidance titled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (the 1998 guidance). The 1998 guidance was issued in response to the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115), which stated that the substantial evidence requirement for effectiveness, which had generally been interpreted as calling for two adequate and well-controlled clinical investigations, could also be met by a single adequate and well-controlled clinical investigation plus confirmatory evidence. The 1998 guidance, among other things, provides examples of the types of evidence that could be considered confirmatory evidence, as

well as a number of illustrations of a single adequate and well-controlled trial supported by confirmatory evidence.

Although the statutory standard for effectiveness had not changed, evolution in drug development and analytical methods since FDA issued the 1998 guidance called for additional guidance to reflect this evolution. Therefore, in 2019, FDA issued the draft guidance titled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" (2019 draft guidance). The 2019 draft guidance complemented and expanded on the 1998 guidance by, among other things, providing more recommendations for development programs targeting diseases that lack effective treatment, rare diseases, and therapies targeting disease subsets where regulatory flexibility in the amount and type of evidence is warranted to meet the substantial evidence standard.

In 2023, FDA issued a draft guidance titled "Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence" (2023 draft guidance). The 2023 draft guidance provides a more comprehensive discussion of meeting the substantial evidence of effectiveness standard with one adequate and well-controlled clinical investigation plus confirmatory evidence, with an emphasis on the quantity and quality of confirmatory evidence.

Advances in our understanding of biological processes and the increasing availability of high-quality data have again transformed the evidentiary landscape for drug development. FDA believes that revising the 2019 draft guidance to reflect these advances is warranted with a focus on approaches to drug development that can yield substantial evidence of effectiveness in the most efficient manner. The revised guidance clarifies how programs across disease areas can rely on one scientifically rigorous adequate and well-controlled clinical investigation with confirmatory evidence to satisfy the substantial evidence of effectiveness standard. It highlights that there are various ways to provide substantial evidence and emphasizes the many factors that can impact the strength of evidence of effectiveness for a drug. These include important

elements of the design, conduct, and analysis of the adequate and well-controlled clinical investigation(s), the clinical and statistical persuasiveness of results, and the characteristics of the overall development program. Whether sponsors have demonstrated substantial evidence will depend on the strength of the evidence provided.

The revised draft guidance retains discussion regarding regulatory flexibility in applying the substantial evidence of effectiveness standard in certain critical settings. FDA's application of flexibility reflects the awareness that somewhat greater uncertainty about effectiveness may be warranted in such critical settings when balanced against the risk of rejecting or delaying the marketing of an effective therapy.

FDA considered comments received on the 2019 draft guidance when revising it. Changes from the 2019 draft guidance include: 1) Streamlining discussion of the history of the substantial evidence of effectiveness standard to focus on current statutory and regulatory requirements. 2) Removing discussion about one trial being the legal and scientific equivalent of two trials, which may have caused confusion about the regulatory status of a clinical investigation. Per the statutory requirements, sponsors relying on one adequate and well-controlled clinical investigation to establish substantial evidence of effectiveness must provide confirmatory evidence. The guidance addresses how such confirmatory evidence may vary depending on the strength of the single adequate and well-controlled clinical investigation. 3) Providing more discussion of meeting the substantial evidence of effectiveness standard with one adequate and well-controlled clinical investigation plus confirmatory evidence across the breadth of development programs.

After finalizing this revised draft guidance, FDA plans to withdraw the 1998 guidance to avoid confusion regarding the Agency's recommendations for meeting the substantial evidence of effectiveness standard. FDA is soliciting comments on any aspects of the 1998 guidance that are not captured in the revised draft guidance and should be captured in the final guidance. The Agency will also consider comments received on the revised draft guidance to inform future

action, which may include further action regarding the 2023 draft guidance. Comments specifically addressing the content of the 2023 draft guidance may be submitted at any time to Docket No. FDA-2023-D-2318. For more instructions on submitting comments to that draft guidance, please refer to the *Federal Register* notice announcing its availability (88 FR 64445).

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products." 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.

As we develop final guidance on this topic, FDA will consider comments on costs or cost savings the guidance may generate, relevant for Executive Order 14192.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. The previously approved 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. 3501-3521). The collections of information in 21 CFR part 312 relating to the investigational new drug applications pathway, which includes clinical trials and clinical trial designs, have been approved under OMB control number 0910-0014. The collections of information in 21 CFR part 314 relating to new drug applications have been approved under OMB control number 0910-0001. The collections of information in 21 CFR part 601 relating to biologic license applications have been approved under OMB control number 0910-0338.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs,

https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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