

and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases.” Dose-finding trials (*i.e.*, trials that include dose-escalation and dose-expansion portions with the primary objective of selecting the recommended phase II dose) for oncology drugs have historically been designed to determine the maximum tolerated dose (MTD). This paradigm was developed for cytotoxic chemotherapy drugs based on their observed steep dose-response, their limited drug target specificity, and the willingness of patients and providers to accept substantial toxicity to treat a serious, life-threatening disease. Most modern oncology drugs, such as kinase inhibitors and monoclonal antibodies, are designed to interact with a molecular pathway unique to an oncologic disease(s) (*i.e.*, targeted therapies). These targeted therapies demonstrate different dose-response relationships compared to cytotoxic chemotherapy, such that doses below the MTD may have similar efficacy to the MTD but with fewer toxicities.

This draft guidance is intended to assist sponsors in identifying the optimal dosage(s) for human prescription drugs or biological products for the treatment of oncologic diseases during clinical development prior to submitting an application for approval for a new indication and usage and does not address selection of the starting dosage for first-in-human trials nor does it address dosage optimization for radiopharmaceuticals, cellular and gene therapy products, microbiota, or cancer vaccines. This guidance should be considered along with the International Conference on Harmonisation (ICH) E4 guidance entitled “Dose-Response Information to Support Drug Registration” when identifying the optimal dosage(s).

This draft guidance is being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on “Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases.” 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.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR parts 50 and 56 have been approved under OMB control number 0910-0130; the collections of information in 21 CFR part 314 have been approved under OMB control number 0910-0001; the collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014; and the collections of information in 21 CFR part 601 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>.

Dated: January 12, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-N-3299]

Understanding the Use of Negative Controls To Assess the Validity of Non-Interventional Studies of Treatment Using Real-World Evidence; Public Workshop; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public workshop; request for comments.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the following public

workshop entitled “Understanding the Use of Negative Controls to Assess the Validity of Non-Interventional Studies of Treatment Using Real-World Evidence.” Convened by the Duke-Margolis Center for Health Policy and supported by a cooperative agreement between FDA and Duke-Margolis, the purpose of this public workshop is to discuss existing negative control methodologies for studies based on real-world data and to outline advantages and disadvantages of the use of negative controls for evaluating the safety and effectiveness of regulated medical products. Additionally, the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research will propose projects to develop negative control methods and implement new tools for use in the Sentinel System, Biologics Effectiveness and Safety (BEST) System, and with Federal Partners.

DATES: The public workshop will be virtually convened on March 8, 2023, from 10 a.m. to 3 p.m., Eastern Standard Time. Either electronic or written comments on this public workshop must be submitted by May 8, 2023. See the **SUPPLEMENTARY INFORMATION** section for registration date and information.

ADDRESSES: The public workshop will be held virtually using the Zoom Platform. The link for the public workshop can be accessed at the following web page: <https://duke.is/cy9w4>.

You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of May 8, 2023. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

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-2022-N-3299 for “Understanding the Use of Negative Controls to Assess the Validity of Non-Interventional Studies of Treatment Using Real-World Evidence.” Received comments, those filed in a timely manner, 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. 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.

FOR FURTHER INFORMATION CONTACT:

Jamila Mwidau, Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 22, Rm. 4481, Silver Spring, MD 20993, 301-796-4989, Jamila.Mwidau@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, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

In connection with the seventh iteration of the Prescription Drug User Fee Amendments (PDUFA VII), incorporated as part of the FDA User Fee Reauthorization Act of 2022, FDA has committed to enhancing and modernizing the FDA drug safety system, including improving the utility of existing tools and adopting new scientific approaches. This commitment includes optimizing the capabilities of the Sentinel Initiative to address questions of product safety and advance the understanding of how Real-World Evidence can be used for studying effectiveness.

Under PDUFA VII, FDA agreed to conduct a public workshop by September 30, 2023, on the use of negative controls for assessing the validity of non-interventional studies of treatment. This public workshop, scheduled for March 8, 2023, will satisfy the PDUFA VII commitment. One purpose of the public workshop is to discuss current negative control methods in studies based on real-world data and discuss future implications for their use to evaluate the safety of regulated medical products. Another

purpose of the public workshop is to present the proposed methods development projects that may support a tool for use in the Sentinel System and BEST.

II. Topics for Discussion at the Public Workshop

Some topics FDA plans to discuss at the public workshop include but may not be limited to the following:

1. What are the strengths and limitations of current negative control methods used in studies based on real-world data?
2. What are known and potential benefits and challenges in using negative controls in evaluating regulated product safety and effectiveness?
3. What additional information is needed about negative control methods to provide confidence regarding their use in regulatory decision-making?

III. Participating in the Public Workshop

Registration: To register for the public workshop, please visit the following website to register: <https://duke.is/cy9w4>. Please provide complete contact information for each attendee, including name, title, affiliation, address, email, and telephone.

Registration is free and open until the public workshop is completed. Persons interested in attending this public workshop can register until 2:59 p.m. Eastern Standard Time on March 8, 2023.

If you need special accommodations due to a disability, please contact margolisevents@duke.edu no later than February 22, 2023.

Dated: January 12, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-P-1982]

Determination That OFIRMEV (Acetaminophen) Injection, 1,000 Milligrams/100 Milliliters (10 Milligrams/Milliliter), Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we)