



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2025-D-1071]

#### **Development of Cancer Drugs for Use in Novel Combination -- Determining the Contribution of the Individual Drugs' Effects; Draft Guidance for Industry; Availability**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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Development of Cancer Drugs for Use in Novel Combination -- Determining the Contribution of the Individual Drugs' Effects.” This draft guidance is intended for sponsors developing drugs for use in combination for the treatment of cancer and provides recommendations for characterizing the safety and effectiveness of individual drugs for use in a novel combination regimen in oncology (i.e., demonstrating the contribution of each drug to the overall effect that is observed for the population). This guidance expands on the recommendations in the 2013 guidance for industry entitled “*Codevelopment of Two or More New Investigational Drugs for Use in Combination*.” This guidance does not address contribution of effect in settings where an investigational drug is being developed in combination with a drug approved for the same indication for the purposes of comparing the approved drug to the combination or to fixed combinations of previously approved drugs for the approved indication(s).

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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-2025-D-1071 for "Development of Cancer Drugs for Use in Novel Combination – Determining the Contribution of the Individual Drugs' Effects." 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 this 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, or Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3103, 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 guidance document.

FOR FURTHER INFORMATION CONTACT: Donna Rivera, Oncology Center of Excellence, Food and Drug Administration, OCE-Guidances@fda.hhs.gov; or Phillip Kurs, Center for Biologics Evaluation and Research, Food and Drug Administration, 240-402-7911.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Development of Cancer Drugs for Use in Novel Combination – Determining the Contribution of the Individual Drugs’ Effects.” This draft guidance describes FDA’s recommendations for characterizing the safety and effectiveness of individual drugs for use in a novel combination regimen (i.e., demonstrating the contribution of each drug to the overall effect that is observed for the population) in treating cancer, including use of data external to a trial for demonstration of contribution of effect for the following types of novel combinations in oncology: (1) two (or more) investigational drugs that have not been previously approved by FDA for any indication; (2) an investigational drug with a drug(s) approved for a different indication; or (3) two (or more) drugs approved for a different indication(s). This guidance expands on the recommendations in the 2013 guidance for industry entitled “*Codevelopment of Two or More New Investigational Drugs for Use in Combination.*”

Combination therapy in oncology is an important treatment modality. Scientific advances have increased our understanding of the pathophysiological processes that underlie many cancers. This increased understanding has provided further impetus to develop new therapeutic approaches using combinations of drugs directed at multiple therapeutic targets to improve treatment response, minimize adverse events, or both. A novel combination of drugs may be considered for development when the necessity of each drug in the proposed combination is supported by a strong biologic rationale including the nonclinical characterization of each drug in the combination and early clinical evidence. A critical aspect of codevelopment of novel combinations of oncology drugs is the characterization of the safety and effectiveness of the individual drugs in the combination because the benefit of using the individual drugs in combination is weighed against the added toxicity when they are used together. In some cases, the conventional approach to demonstrating contribution of effect by employing a standard factorial design may be infeasible. Therefore, FDA is providing recommendations regarding the use of external data for demonstrating the contribution of the individual drugs to the effect of a combination regimen and the key aspects to consider including selection of data source(s) and endpoints, and suitability of a data source.

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 "Development of Cancer Drugs for Use in Novel Combination – Determining the Contribution of the Individual Drugs' Effects." 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 (PRA) (44 U.S.C. 3501-3521). The collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014; the collections of information in 21 CFR part 314 have been approved under OMB control number 0910-0001; 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 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: July 14, 2025.

**Grace R. Graham,**

*Deputy Commissioner for Policy, Legislation, and International Affairs.*

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