



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2025-D-6131]

General Considerations for the Use of New Approach Methodologies in Drug Development; Draft Guidance for Industry; Availability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SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing the availability of a draft guidance for industry entitled “General Considerations for the Use of New Approach Methodologies in Drug Development.” The purpose of this draft guidance is to provide drug developers with a validation framework and general recommendations for using new approach methodologies (NAMs) in drug development. Although animal toxicity studies have proved to be a critical method to identify potential risks to human health, finding ways to improve human relevance while reducing the use of animals by developing reliable NAMs furthers an important Center for Drug Evaluation and Research (CDER) priority to move away from reliance on animal testing. The recommendations in this draft guidance are intended to highlight scientific principles of study design and reporting that can be applied broadly and flexibly in the validation of NAMs used in drug development. This draft guidance is not intended to address specific NAMs and does not address the use of NAMs in drug discovery; rather, it encourages the use of NAMs in regulatory submissions, especially when they improve the predictivity of nonclinical studies for increased safety in clinical trials.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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-6131 for "General Considerations for the Use of New Approach Methodologies." 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 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: Nakissa Sadrieh, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 22, Rm. 6163, Silver Spring, MD 20993, 240-402-2194.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “General Considerations for the Use of New Approach Methodologies.” This guidance describes CDER’s general recommendations to consider for validating NAMs when nonclinical NAMs data are provided in support of a drug application or regarding an order issued under section 505G of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for an OTC monograph. This includes OTC monograph orders issued under section 505G of the FD&C Act for nonprescription drugs intended for topical administration. Among other things, this guidance is issued in compliance with the requirement that FDA issue a new draft guidance on nonclinical testing alternatives to animal testing for OTC monograph drugs intended for topical administration under section 505G(r)(2)(B).

As part of the Consolidated Appropriations Act, 2023 (Pub. L. 117-328), the Food and Drug Omnibus Reform Act provided increased clarity to stakeholders regarding the potential use of new approach methodologies to support nonclinical data packages in investigational new drug applications. Specifically, section 3209(a) of the Consolidated Appropriations Act, 2023 amended section 505(i) of the FD&C Act to clarify that nonclinical tests can be used to support

proposed clinical testing. Section 3209(a) further amends the FD&C Act by defining “nonclinical test” as “a test conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug” and provides examples, including cell-based assays, organ chips and microphysiological systems, computer modeling, other nonhuman or human biology-based test methods (such as bioprinting), and animal tests.¹

FDA’s current regulatory framework permits and encourages the use of NAMs, as described in existing regulations and guidance. CDER has developed this guidance document to further encourage the submission of NAM data.

This guidance, when finalized, will provide key considerations related to the validation of NAM data, to help ensure data quality and reliability and to support regulatory decision-making by CDER. The considerations provided in this draft guidance reflect recent developments in validation frameworks for NAMs. FDA’s goal in issuing this draft guidance is to help facilitate the development and use of validated NAMs that accurately predict risks to human health, while also decreasing usage of animal testing. This draft guidance includes general validation considerations for industry, focusing on context of use, human biological relevance, technical characterization, and how to demonstrate that a NAM is fit-for-purpose. This guidance is intended to encourage the submission of NAMs and early engagement with drug review divisions. This guidance is not intended to address specific NAMs and does not address the use of NAMs in drug discovery.

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 “General Considerations for the Use of New Approach Methodologies in Drug Development.” It does not establish any rights for any person and is not binding on FDA

¹ Section 505(z) of the FD&C Act (21 U.S.C. 355(z)).

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 314 pertaining to the submission of new drug applications have been approved under OMB control number 0910-0001. The collections of information in 21 CFR part 312 pertaining to the investigational new drug applications have been approved under OMB control number 0910-0014. The collections of information in 21 CFR part 601 pertaining to the submission of biologics license applications have been approved under OMB control number 0910-0338. The collections of information in 21 CFR 58 pertaining to good laboratory practice for nonclinical laboratory studies have been approved under OMB control number 0910-0119.

III. Electronic Access

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